STATISTICAL INTERPRETATION OF A VETERINARY HOSPITAL DATABASE: FROM DATA TO DECISION SUPPORT

by

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ABSTRACT

Research was undertaken to investigate whether data maintained within a veterinary hospital database could be exploited such that important medical information could be realised. At the University of Glasgow Veterinary School (GUVS), a computerised hospital database system, which had maintained biochemistry and pathology data for a number of years, was upgraded and expanded to enable recording of signalment, historical and clinical data for referral cases. Following familiarisation with the computerised database, clinical diagnosis and biochemistry data pertaining to 740 equine cases were extracted. Graphical presentation of the results obtained for each of 18 biochemistry parameters investigated indicated that the distributions of the data were variable. This had important implications with respect to the statistical techniques which were subsequently applied, and also to the appropriateness of the reference range method currently used for interpretation of clinical biochemistry data. A percentile analysis was performed for each of the biochemistry parameters; data were grouped into ten appropriate percentile band intervals; and the corresponding diagnoses tabulated and ranked according to frequency. Adoption of a Bayesian method enabled determination of how many times more likely a diagnosis was than before the biochemistry parameter concentration had been ascertained. The likelihood ratio was termed the "Biochemical Factor". Consequently, a measurement on a parameter, such as urea, could be classified on the percentile scale, and a diagnosis, such as hepatopathy, judged to be less or many times more likely, based on the numerical evaluation of the Biochemical Factor.

One issue associated with the interrogation of the equine cases was that the diagnoses were clinical in origin, and, because they may have been made with the assistance of biochemistry data, this may have yielded biased results. Although this was considered unlikely to have affected the findings to a large extent, a database containing biochemistry and *post mortem* diagnosis data for cattle was also assessed. The combination of percentile analysis and probabilistic techniques was similarly applied to 796 cattle cases, the advantage being that the *post mortem* diagnoses had been made independently of the biochemistry data. The differential diagnoses and associated Biochemical Factors were determined within each percentile band for each of 14 biochemistry parameters. The results achieved from analysis of the bovine cases were further employed to generate biochemistry profiles for each of the five most common diseases. Although the disease profiles differed, they were assessed using 350 test cases, and this indicated that the approach could not be used with sufficient accuracy to classify new cases into appropriate disease categories. However, a smaller focused study was initiated to assess the ability of laboratory parameters to differentiate between cattle with acute and chronic inflammation. Multivariable analysis was employed and revealed that serum amyloid-A best classified the cattle cases into appropriate groups, a finding of possible importance for clinical care and meat hygiene.

Following generation of such results, it was important that a means for conveying the information be established. The results from analysis of the equine and bovine populations which enabled a clinician to establish whether a biochemistry result was abnormal, the degree of abnormality, and the most likely associated diagnoses, formed the basis of a decision support system. The Microsoft Windows application assists the clinician in diagnosis and management of cases, and the approach is equally relevant to other species. More importantly, the contribution was considered a step towards the provision of objective interpretation of clinical biochemistry data in the veterinary domain, and responded to the challenge of translating data into decision support.

DECLARATION

I declare that this thesis describes work carried out by me, except for those matters mentioned specifically in the acknowledgements. It has not been submitted in any form for another degree or professional qualification.

KATHRYN M.G. KNOX

Parts of this thesis have been accepted for publication or presentation elsewhere.

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First, the work undertaken in this thesis would not have been possible without the foresight of a group of pathologists at the University of Glasgow Veterinary School who appreciated the potential value of storage and retrieval of veterinary medical data within the hospital environment. Although establishment of the integrated computerised system, incorporating the clinical, pathological and biochemical data central to this thesis, was an important accomplishment; the continued time and effort invested by pathologists, clinicians and biochemists, of the Departments of Veterinary Pathology and Veterinary Clinical Studies, respectively, in updating the system, enabled the work presented.

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The nature of this thesis dictated that computers play a large part in my day to day work, and, in this respect, I am eternally grateful to members of the Veterinary Informatics and Epidemiology Group, Colin Naismith, David Irvine, Tom Irwin and Vicki Dale, for their unending patience in assisting with inevitable trouble-shooting. In

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This thesis is dedicated to my mum, for her continued support,
and to my dad, who would have been so proud.

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LIST OF ACRONYMS

AGP	α_1-acid glycoprotein
Alb	Albumin
AP	Alkaline phosphatase
AST	Aspartate amino-transferase
BASO	Basophil
BPMN	Band polymorphonuclear cell
CPK	Creatinine phosphokinase
ESO	Eosinophil
g	gram
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
Glob	Globulin
GUVS	University of Glasgow Veterinary School
Hb	Haemoglobin
HP	Haptoglobin
l	litre
LYM	Lymphocyte
m	milli
MONO	Monocyte
PCV	Packed cell volume
PMN	Polymorphonuclear cell
RBC	Red blood cell
SAA	Serum amyloid-A
SI	Similarity Index
TP	Total protein
µ	micro
U	Units
WBC	White blood cell

CHAPTER I

INTRODUCTION

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"A computer isn't able to do anything a person can't do, but it can do it a lot faster and it does have a better memory."

Frederick Rude (1986)

1.1 INTRODUCTION

As the new millennium approaches, there is a tendency to reflect on achievements, innovations and creations of years past. Undoubtedly, one of the more recent developments which has reformed the functioning of the modern world has been that of computerisation. From the development of space-craft which delivered man to the moon, to the microchip which ensures refrigerators remain at a specified temperature, life without computers is almost inconceivable.

The introduction of computerisation to the fields of human and veterinary medicine has vastly improved the ability to store, retrieve and manipulate data. The development of dedicated databases for the recording of medical information has facilitated the performance of epidemiological studies. Only through the existence of a computerised hospital database, has the work undertaken within this thesis been possible.

1.2 BACKGROUND

At the University of Glasgow Veterinary School (GUVS), individual computerised databases containing biochemistry and pathology data had been maintained since 1975 and 1985, respectively (Gettinby *et al.*, 1991). The wide-ranging and comprehensive pathology database formed the foundation for a hospital-wide computerised network. This included hardware standards, software standards, and the coding system established by the Department of Veterinary Pathology, under the directorship of Professor William Jarrett. In 1988, the information within the pathology and biochemistry databases was uploaded to an integrated relational database system which was to maintain signalment, clinical, biochemical, microbiological, haematological and pathological information

relating to all referral cases which presented to the Veterinary School hospital. This heralded a new era in data maintenance at GUVS.

The database system was designed to facilitate data entry and retrieval. However, after several years of maintaining the database, there was speculation as to whether the database was being used to its full potential. Indeed, many years' worth of valuable information had been maintained within the database, and yet little effort had been invested in ascertaining whether the information was of any scientific value or how its potential could be best realised.

The general remit of the project outlined in this thesis was to interrogate the database in an attempt to discover whether the raw data could be transformed into useful information.

1.3 THESIS OUTLINE

The second chapter in the thesis reviews the literature pertaining to the development of data recording systems in the veterinary domain. From early systems, such as hand-written day-books, through to more complex networked computerised systems, advantages and disadvantages of each method are highlighted.

The methods of data recording which have been adopted for the maintenance of information relating to referral cases which have presented to GUVS are discussed in Chapter 3. The emphasis of the chapter is on the DataFlex (Data Access Corporation, Miami, Florida, USA) relational database system which was in use for storage and retrieval of data at the time of writing. Following an outline of the system structure, capabilities and operation commands, a brief summary of the data stored within the system is presented.

Chapters 4 and 5 outline the application of statistical techniques to plasma biochemistry and associated diagnosis data, for equine and bovine cases, respectively. In particular, a combination of percentile analysis and Bayesian probabilistic approaches are used to generate useful information from the raw data. Discussion centres on the current means for the interpretation of clinical biochemistry data, based on a reference interval, and, further, offers new methods for interpretation, based on the results of the interrogation of the hospital database.

Given that plasma biochemistry testing is carried out not only to assess the health status of an animal, but also for the clinician to confirm or deny diagnostic suspicions, the development of biochemistry profiles for several cattle diseases is outlined in Chapter 6. The profiles are compiled by presenting the results of the statistical analysis undertaken in Chapter 5 in a different manner. The profiles give a visual picture of the biochemistry results which were obtained for the cattle cases which presented to GUVS with the specific diseases in question. A random selection of cattle cases is used to assess the performance of the disease profiles.

Chapter 7 involves a subset of the GUVS cattle population, and stems from work undertaken by Drs Neil Horadagoda and David Eckersall from the section of Veterinary Clinical Biochemistry, Department of Veterinary Clinical Studies. The project was initiated to investigate the ability of clinical laboratory parameters to differentiate between cattle with acute and chronic inflammatory processes. As opposed to the datasets under investigation in Chapters 4, 5 and 6, in which animals are classified as suffering from one of many different diseases; the dataset in Chapter 7 divides cattle into only two groups, cattle with acute or chronic inflammatory processes. Multivariable logistic regression analysis and receiver operating characteristic (ROC) curve analysis are performed to investigate the differentiating ability of the laboratory parameters. Discussion focuses on the impact of the results in terms of meat hygiene and cattle care.

Chapter 8 outlines the development of a decision support software system which emanated from the interrogation of the hospital database. A basic outline of the construction of the software and of the final design are given. Implications for the use of such a decision support system are highlighted, with respect to both the individual clinician, and more widely in veterinary medicine as a whole.

Finally, general conclusions pertaining to the use of a hospital database in the quest for valuable information relating to disease in the veterinary domain are detailed in Chapter 9. The pathway from simple raw data to the development of decision support is summarised, and discussion emphasises the implications for the future of computer technology in terms of improving patient care in the field of veterinary medicine.

CHAPTER II

DEVELOPMENT OF DATA RECORDING SYSTEMS IN THE VETERINARY DOMAIN

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"The practice must maintain an efficient system of documenting and filing records of case histories of all patients."

RCVS Guide to Professional Conduct (1996)

2.1 DATA STORAGE IN THE FIELD OF MEDICINE

In the past few decades, there has been an increase in public demand for improved health care and attention in the domains of both human and veterinary medicine (Pollock and Fredericks, 1988; Thrusfield, 1995). Through development of communication technology, such as television, radio and paper media, the general public is increasingly aware of medical issues. This awareness ranges from an understanding of the basic structure of the medical system, through to knowledge of newly discovered diseases and breakthroughs in modes of therapy, although the latter two are often limited. In order to satisfy the expectations of the modern client and patient, each and every medical case must be approached methodically and managed efficiently. One method of improving efficiency and ultimately health care in the medical domain is through enhanced data storage.

In the field of medicine, patient-based data storage at its most basic level is in the form of a "medical record". In both human and veterinary medicines, the importance of a well-maintained medical record is paramount (Pritchard, 1978; Duppong and Ettinger, 1983; Thrusfield, 1985; Millman *et al.*, 1996). This is true, whether it be on an individual level, or on a group or herd level. Within recent decades, the requirements for the maintenance of medical records have become increasingly stringent (Saidla, 1976). In the United States, the maintenance of veterinary medical records is a legal requirement, the details of which may vary from State to State (Pritchard, 1978; Hannah, 1991). In the United Kingdom, although the maintenance of clinical records is not a legal requirement, Section 6.2.4.h of the Royal College of Veterinary Surgeons (RCVS) Guide to

Professional Conduct (1996) states, "The practice must maintain an efficient system of documenting and filing records of case histories of all patients". Failure to do so may result in withdrawal of licence to practice in the United Kingdom.

2.1.1 Functions of the medical record

The veterinary medical record is maintained for a number of reasons. The primary function of a medical record is to provide documentation of a patient's health status and care (Thrusfield and Hinxman, 1981; Duppong and Ettinger, 1983). The medical record is generally instigated at the time of birth, or within the first few weeks of life, and is updated as necessary throughout the lifetime of the patient. The individual record contains information pertaining to the identification of the patient, vaccination history, and past and current periods of illness (Duppong and Ettinger, 1983; Thrusfield, 1985).

The second function of the medical record is to provide a means of information exchange among veterinarians. In the veterinary domain, knowledge of physiological processes, disease mechanisms and modes of therapy has increased significantly (Pollock, 1986; Thrusfield, 1995). This has led to increased specialisation, with respect both to species-specific work and to disciplines within species; for example, a small animal orthopaedic specialist (Fessler, 1984a; Gerrard and Little, 1994; Henderson, 1997). The increasing popularity of RCVS certificates and diplomas offers further evidence of this trend (RCVS Registers and Directory, 1997/1998). In general veterinary practice, there has been a move away from the one-person mixed practice towards the creation of larger practices, where each veterinarian has a particular, possibly species-specific, role (Sheridan, 1997a; Sheridan, 1997b). The greatest advantage of this practice-based development is the maximisation of resources, both human and material. However, it must be appreciated that any animal patient entering such a large practice may be seen a number of different veterinarians, perhaps even for the same problem or possibly for a different episode of disease. In such an environment, the medical record permits continuity of care by promoting communication between veterinary colleagues (Duppong and Ettinger, 1983).

Thirdly, the maintenance of comprehensive medical records can be used for teaching and research purposes (Thrusfield, 1983a; Thrusfield, 1983b; Ribble *et al.*, 1990; Little *et al.*, 1994). Interestingly, Pritchard (1978) stated that there was a strong correlation between the quality of clinical teaching programs, in both human and

veterinary medicine, and the quality of medical records of the institution. This is perhaps directly a reflection of clinical teaching staff who are efficient and thorough in their day-to-day work, whether it be maintaining case records or teaching. On an individual level, medical records may be used for teaching students about a particular disease condition, or the approach to an unwell animal, by following through a medical record and tracing the course of the events. Collectively, medical records can be used for epidemiological studies (Thrusfield, 1983a; Zwetsloot-Schonk, 1990; Talbot and Mills, 1994). It follows therefore that the more comprehensive and reliable the raw data, the more valuable the results of any study conducted (Pollari *et al.*, 1996).

Finally, the medical record may be used in a situation where a doctor or veterinarian has to provide documentary evidence to defend his or her actions in a court of law (Pritchard, 1978; Duppong and Ettinger, 1983; Hannah, 1991; Millman *et al.*, 1996). Broadsheet newspapers have highlighted instances in the medical field where lack of communication among doctors has resulted in poor patient care, often in emergency situations. Such instances highlight the requirement, both from a legal point of view and from the aspect of patient care, for well maintained medical records.

2.2 VETERINARY CLINICAL DATA

The veterinary medical record may be as simple or as complicated as is necessary. Currently, in the United Kingdom there are no official detailed guidelines as to how the individual medical record should be structured. Thus, the details of the record depend largely on the requirements and policies of individual practices or hospitals. For the maintenance of useful records, however, the types of information which may be stored are numerous (Duppong and Ettinger, 1983; Miller, 1996). The animal identification itself should contain the following information: name, species, breed, date of birth/ age and gender. Basic details to identify the animal's owner are also required for contact purposes: name, address and contact telephone number. Other types of information which may be maintained within the medical record relate more specifically to the health status of the animal at any particular time. Most of the domestic species, both companion animal and production animal, undergo veterinary inspection as healthy animals, whether for neutering, vaccination or health screening. Thus, even those animals which remain "healthy" throughout their lives have a medical record. It is during periods of illness that the medical record becomes potentially complicated. The types of information which may

be collected include: history, clinical examination, details of further tests, test results, differential diagnoses, treatment instigated, prognosis and outcome. These details may be obtained during one visit, or, more usually, over a number of visits. It is therefore important that the medical record be structured such that the course of events can be readily followed. From this very brief outline of the types of veterinary clinical data which may be collected, it is apparent that the design of a recording system, in which such data can be readily input and retrieved, may be complex.

2.3 METHODS OF STORING VETERINARY CLINICAL DATA

Due to expansion of knowledge in the medical field, the means of recording clinical data have also had to develop and expand. Increasingly, practising veterinarians and research workers appreciate the necessity of well-maintained hospital and practice databases (Thrusfield, 1983a; Ribble *et al.*, 1990; Thrusfield, 1995). The move from a few pencilled notes in the consulting room to the age of computerised relational databases has transformed data collection in the veterinary domain.

2.3.1 Day-book

The original means of documenting information about veterinary medical cases was the day-book (Thrusfield, 1983b). Within a large sturdy notebook, brief written notes about individual animals were maintained. There was little structure to the record, the notes recorded being mainly free text. The book was maintained on a day-to-day basis, rather than a patient basis. This meant that data retrieval was extremely laborious and time-consuming. It was difficult to follow the history of any individual patient who was seen over a number of visits because its details were separated by the other animals which had been seen in between times. This was inefficient and may have resulted in inadequate animal care. As with any system which involves hand-written input, legibility was a potential problem. There was only one copy of the day-book, so if it were to be misplaced or damaged, all the records would be lost. This system is now more or less obsolete (Thrusfield, 1983b).

2.3.2 Record cards

In the record card system, each patient is allocated a record card (Figure 2-1). The front of each record card details owner and animal identification, usually at the top, and the

remainder of the card is for medical details. The medical details are entered chronologically, the record expanding each time the animal visits, resulting in a card detailing the animal's complete medical history. Entry of information to the record is hand written free text. When not in use, the records are filed, often in alphabetical order, in drawers or boxes (Thrusfield, 1983b). It is important that the card used for the records is of reasonable standard because the records have to endure a lot of manipulation.

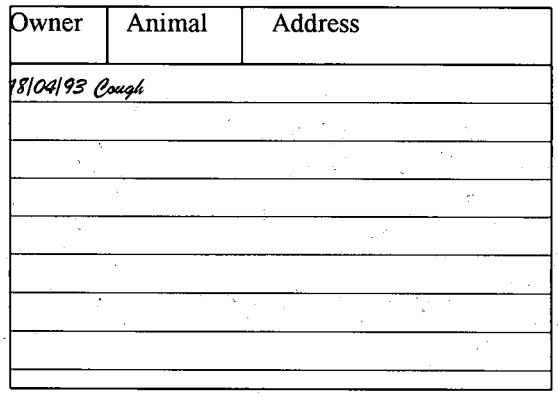


Figure 2-1 Example of a record card for storing free text hand-written medical information pertaining to veterinary cases.

The record card system offers a number of advantages over the day-book system. The records are stored alphabetically by the owner's name, thus facilitating access. The animal's full medical history is readily available. Coloured flags may be used to further enhance the system (Thrusfield, 1985). If a coloured flag is at the front of the record, the consulting veterinarian is immediately alerted to one or more important features pertaining to the animal. The details of such a flagging system vary from practice to practice, but may be used to indicate, for example, an epileptic animal, previous drug sensitivities, cardiovascular compromise, aggression, and so on. This system helps to ensure that each animal receives appropriate attention and treatment.

There are, however, a number of disadvantages of the record card system - both physically and conceptually. The records themselves can be prone to damage, especially those for animals undergoing long-term treatment and requiring many visits, when the card, with no outer protection, may be frequently filed and refiled. For animals with a long medical history, the record can become rather expansive, with several cards stapled together or held together with treasure tags. There is a risk that such records may come apart and that pages may be lost, resulting in potentially useless records.

Over a period of years, in a large practice the record card system can become rather bulky. With alphabetical filing, the expansion of the system is from the middle, i.e. the S - surname records impinge on the space originally for T - surnames, rather than new cases being added on at the end of the filing system. This results in the requirement for regular repositioning of the filed records. This is an inefficient use of time, and also increases the likelihood of loss of records (Duppong and Ettinger, 1983). Further disadvantages associated more directly with alphabetical filing include the proclivity with which names may be misspelled and thus misfiled and the necessity to search through a vast number of records within one of the more popular surnames (Willen, 1976). These issues may addressed to some extent in those systems which colour code the alphabet, thus visually representing at least the first initial of the surname (Duppong and Ettinger, 1983).

The alphabetical filing system, where records are stored under the owner's name rather than under an animal identification, tends to encourage the maintenance of family records as opposed to individual animal records (Duppong and Ettinger, 1983). This means that the records for each of possibly several animals owned by one person are maintained within the same record card. This may be advantageous in the event of a group problem, such as a flea infestation, affecting each member of a household. However, often the problems relate to only one animal, and the maintenance of joint records may lead to confusion. Some practices offer individual cards for each animal within the owner record in an attempt to abate this problem (Duppong and Ettinger, 1983).

With regard to entering patient data, the record card is almost entirely unstructured. Apart from patient identification details, often entered by secretarial staff, the record card is usually left blank for the medical details. The entries are hand-written which can lead to legibility problems, especially between different veterinarians and nurses; and consist of brief, unorganised notes about those features the veterinarian deemed important during the consultation. Such records may lack consistency and may result in clinical oversights in patient care due to the potentially unstructured approach to patient assessment (Willen, 1976). The record card system offers no form of back-up, and if a record is misplaced the medical history is lost.

Despite these disadvantages, the record card system has been a popular means of recording case data in general veterinary practice (Thrusfield, 1983b). The record card

system is, however, rarely employed in larger practices and teaching institutions. This may be partly a reflection of the inability of the system to function efficiently in an institution with a large case-load, but may be also a refection of the limitations of the system with respect to research. For epidemiological studies, medical records must be both comprehensive and readily searched. The record card system makes no provision for either consistency or completeness of record content or for searching, and is, therefore of limited use in the research environment.

2.3.3 Punched cards

The punched card system provides a means of coding data such that simplistic record searches may be carried out. There are two types of punched card systems: the edge-punched and the centre-punched (Thrusfield, 1983b).

2.3.3.1 Edge-punched cards

In the edge-punched system, each animal is represented by a card, which contains its identification details (Figure 2-2). Around the edge of the card are a number of holes, each representing a clinical attribute, such as cough or diarrhoea. When an animal presents to the veterinarian, the various attributes it demonstrates are punched. By a simple mechanical technique, the punched card system allows elementary medical record searches to be carried out. If, for example, a veterinarian wishes to review all those cases which presented with a cough, when a long needle is passed through the cough attribute hole for a group of case records, the records which have had "cough" punched will not be picked up, and will drop out when the needle is lifted. This method provides a simple, inexpensive means of interrogating case records, but has a number of disadvantages. The number of attributes which can be represented by holes around the medical record card is limited. Once the attributes have been assigned to a hole, the system can not be altered without recoding all previous records. Carelessness may lead to the incorrect hole being punched, losing the value of attribute searches. The edge of the card is subjected to significant handling, and when it becomes mis-shapen, the simplistic search technique may fail. The number of case records which can be searched at any one time is limited, thus the time taken to search through records in a large practice could be prohibitive.

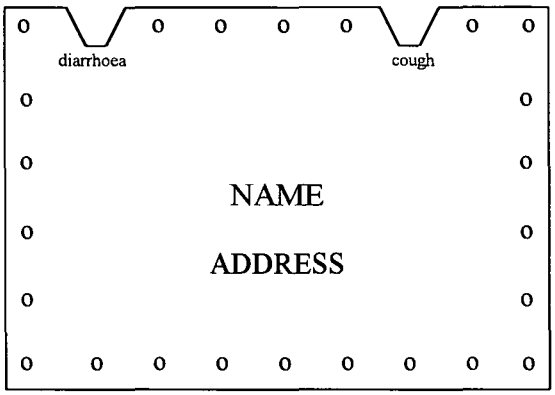


Figure 2-2 Example of an edge-punched record card for storing medical information pertaining to hospital cases.

2.3.3.2 Centre-punched cards

In the centre-punched system, attributes, rather than animals, are represented by cards (Thrusfield, 1983b). These attributes may be related to breed, clinical signs, diagnoses, treatments, or whatever the practice deems important. On the front of each attribute card is an extensive array of numbers which represents individual animal patients in a coded numerical format (Thrusfield, 1985). When a patient has a certain attribute, then its number is centre-punched out of that attribute card (Figure 2-3). By laying a selection of various feature cards on an illuminated screen, animals which have those features may be identified as those which have been punched each and thus allow the light to pass through. Although this system provides a means of interrogating case records, the searches it allows are limited and the equipment for punching the centre holes is expensive (Thrusfield, 1985).

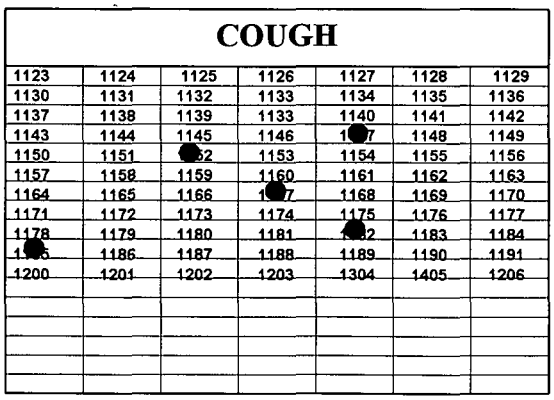
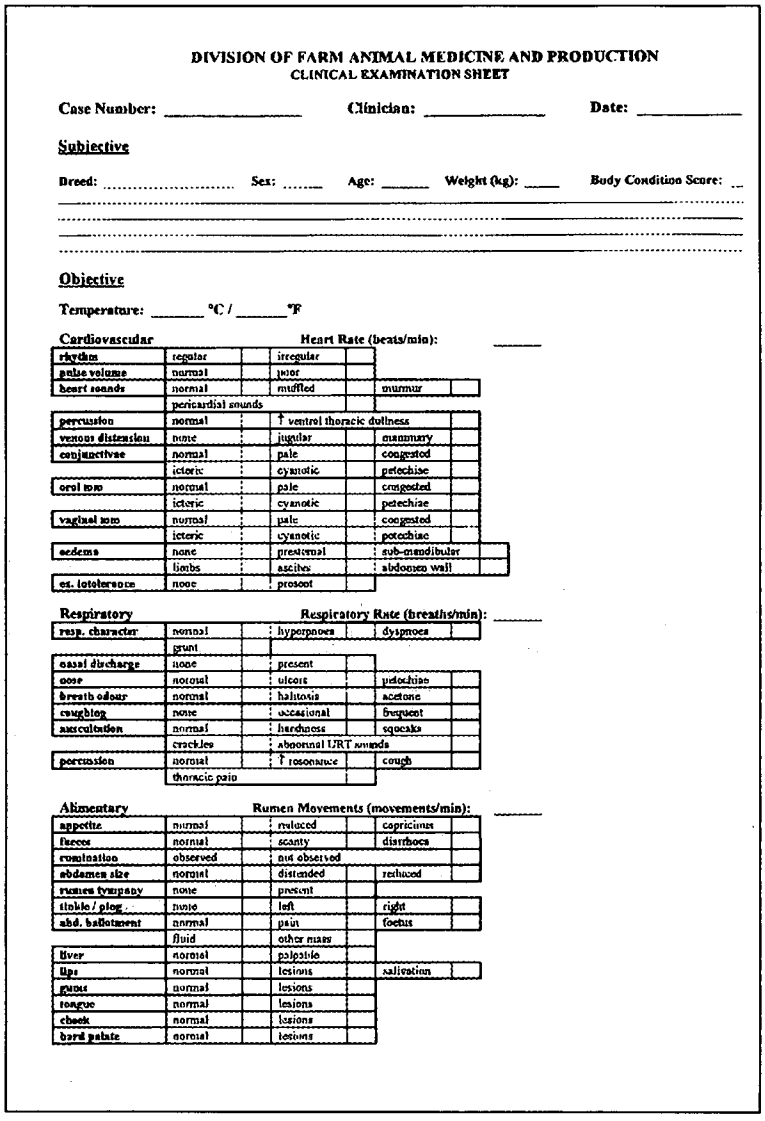


Figure 2-3 Example of an centre-punched record card for storing medical information pertaining to veterinary cases.

These punched card systems have been used in the veterinary environment, but have been superseded by more sophisticated recording systems.

2.3.4 *Pro formas*

The development of the *pro forma* was a move towards the maintenance of complete, comprehensive medical records. It is a partially closed record system, with sheets consisting of different checklists and also of blank areas for free text entries if required (Figure 2-4) (Thrusfield, 1985). The checklists may be very simple and contain only information pertaining to vaccination status, but may be as comprehensive as to cover most of the eventualities of a historical or clinical examination. Each medical record may consist of a number of A4 paper sheets, relating to different aspects of a case, such as history, clinical examination or diet, with all the sheets maintained in a sturdy envelope or plastic folder (Duppong and Ettinger, 1983). Often, a numerical case identification and filing system is adopted. That is, each animal is given a unique hospital number, and all new cases are allocated the next number chronologically. An animal maintains this hospital number throughout its life. An owner-patient index must be maintained with this system, so that the patient case number can be retrieved from the owner's name (Duppong and Ettinger, 1983).



DIVISION OF FARM ANIMAL MEDICINE AND PRODUCTION
CLINICAL EXAMINATION SHEET

Case Number: _____ Clinician: _____ Date: _____

Subjective

Breed: ..... Sex: ..... Age: _____ Weight (kg): ____ Body Condition Score: __

Objective

Temperature: _____ °C / _____ °F

Cardiovascular — Heart Rate (beats/min): _____

rhythm	regular		irregular			
pulse volume	normal		poor			
heart sounds	normal		muffled		murmur	
	pericardial sounds					
percussion	normal		↑ ventral thoracic dullness			
venous distension	none		jugular		mammary	
conjunctivae	normal		pale		congested	
	icteric		cyanotic		petechiae	
oral mm	normal		pale		congested	
	icteric		cyanotic		petechiae	
vaginal mm	normal		pale		congested	
	icteric		cyanotic		petechiae	
oedema	none		pectoral		sub-mandibular	
	limbs		ascites		abdomen wall	
cr. tolerance	none		prosoot			

Respiratory — Respiratory Rate (breaths/min): _____

resp. character	normal		hyperpnoea		dyspnoea	
	grunt					
nasal discharge	none		present			
nose	normal		ulcers		petechiae	
breath odour	normal		halitosis		acetone	
coughing	none		occasional		frequent	
auscultation	normal		harshness		squeaks	
	crackles		abnormal URT sounds			
percussion	normal		↑ resonance		cough	
	thoracic pain					

Alimentary — Rumen Movements (movements/min): _____

appetite	normal		reduced		capricious	
faeces	normal		scanty		diarrhoea	
rumination	observed		not observed			
abdomen size	normal		distended		reduced	
rumen tympany	none		present			
ttable / plog	none		left		right	
abd. ballotment	normal		pain		foetus	
	fluid		other mass			
liver	normal		palpable			
lips	normal		lesions		salivation	
gums	normal		lesions			
tongue	normal		lesions			
cheek	normal		lesions			
hard palate	normal		lesions			

Figure 2-4 An example of part of a *pro forma* medical record used for recording clinical information. This *pro forma* paper record is used in the Division of Farm Animal Medicine and Production at GUVS.

The *pro forma* medical record system offers a number of advantages. The *pro forma* encourages consistency of medical records. With a checklist to complete, certain pieces of information about each case will always be recorded, regardless of the presenting problem. Not only is this advantageous with respect to the production of comprehensive data for epidemiological studies, it may also serve to prompt veterinarians to inquire about aspects of a case they may have neglected to consider. This may be particularly useful for the inexperienced clinician. Checklists also reduce the requirement to decipher hand-written notes, and therefore ensure consistency of care if the animal is presented to a different veterinarian on a subsequent visit. Numerical filing is preferred to alphabetical filing because of the increased accuracy in filing and retrieval (Willen, 1976; Duppong

and Ettinger, 1983). Furthermore, allocation of an individual hospital number to each case negates any confusion which may arise when medical records for family pets are grouped together.

As with most medical record storage systems, there are a number of disadvantages. The checklists can be very time-consuming to complete, and can be low on the list of busy clinicians' priorities. Some veterinary clinicians view the information as irrelevant, and thus the forms are sometimes left unfinished. For those records which consist of a number of paper sheets within an envelope or folder, there is a risk that some of the sheets from within the record may be mislaid, resulting in an incomplete medical record. Although the numerical filing system is an improvement, it is not infallible. It is very easy to mistake, for example, case number 112322 for 112232, resulting in misfiling, and ultimately loss of the record (Willen, 1976; Duppong and Ettinger, 1983). There is no form of back-up, so missing files are irretrievable. With only one copy, if one veterinarian is reviewing the case, the record is not available for others. Over a period of time, the system may become bulky (Rude, 1986), and consequently it may be necessary to have a separate storage area where files used less often can be kept. Although the *pro forma* medical record provides comprehensive data for epidemiological studies, there is no ready means of searching the case records, a potential hindrance to research (Thrusfield and Hinxman, 1981).

2.3.5 Problem oriented records

The problem oriented medical record system is a concept developed by Dr. Lawrence Weed (Saidla, 1976; Willen, 1976). It has been widely used in human medicine and was introduced to the veterinary domain in the mid 1970s (Willen, 1976; Saidla, 1978; Stitt, 1996). The problem oriented medical record presented a new approach to the animal patient with respect to case management and gathering of veterinary clinical data. The system encourages a logical approach to diagnosis and management of a case, and maintenance of well-structured medical records. The problem oriented medical record (POMR) promotes identification of the problems from which the animal patient is suffering, assessment of those problems, formulation of a plan of action for management of the problems and then following the progress of the case. The record has four basic components, namely, database, problem list, plan, progress notes (Figure 2-5) (Saidla, 1983; Stogdale, 1984; Thrusfield, 1985; Bushby, 1988).

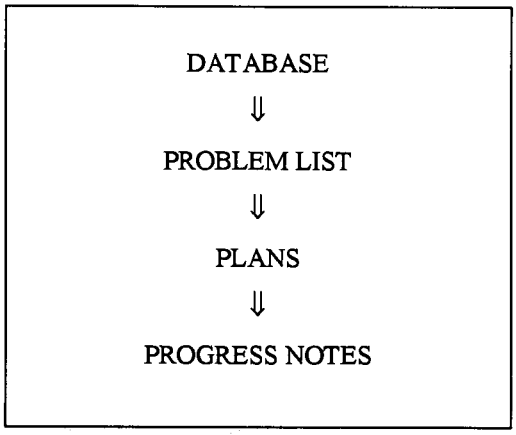


Figure 2-5 The four basic components of the problem-oriented medical record, namely, database, problem list, initial plans and progress notes.

The extent of the database is defined by the veterinarian or by practice policy (Stogdale, 1984). The database contains all information gathered about the case, possibly using a *pro forma* approach. It may include details such as signalment, primary complaint, history, clinical examination and further test results (Saidla, 1978; Thrusfield, 1983b). Different databases may be established for different classes of patient, such as paediatrics, adults or emergencies, each designed to ensure an appropriate defined minimum of data is always recorded (Saidla, 1978).

The problem list usually constitutes the cover page of the medical record, and serves as an index for the entire medical record (Saidla, 1976). The problems are listed in chronological order, with the date on which the problem was first observed, and, if appropriate, the date on which the problem resolved. Saidla (1983) broadly defined a problem "...as anything that interferes with the patient's well-being and requires management or further evaluation". The problem may be a definitive diagnosis, but more often, will be a clinical sign or abnormal laboratory result. The problem list is updated as some problems resolve, and new problems appear. It serves as an excellent summary of a patient's medical history, and is easily reviewed each time the animal presents, either to the same veterinarian, or a different veterinarian (Willen, 1976; Stogdale, 1984). Once the database and the problem list have been established, the plan of action is formulated.

The initial plans may be numbered to correspond to each problem identified, and may include further diagnostic tests to help differentiate between a number of possible

diagnoses, therapy to be instigated or advice to the owner (Saidla, 1978; Thrusfield, 1983b).

The fourth component of the POMR is composed of the progress notes section. The progress notes should be dated and titled to correspond with the problem list (Saidla, 1978), and are compiled using the SOAP acronym, a format used within the Weed system to represent Subjective data, Objective data, Assessment and Plan, as detailed in Figure 2-6 (Willen, 1976; Saidla, 1978; Thrusfield, 1983b).

***S**ubjective data*	Information supplied by the owner, i.e. case history.
***O**bjective data*	Information gleaned by veterinarian, i.e. results of clinical examination, laboratory results, X-ray reports, etc.
***A**ssessment*	Assessment of the animal using all available information.
***P**lan*	Steps required to solve/ manage the problem.

Figure 2-6 Outline of the SOAP acronym used in the composition of progress notes within the problem oriented medical record.

Flow sheets are sometimes used within the progress notes to allow presentation of certain results in graphical format, rather than as narrative text (Saidla, 1978). For example, the plasma concentration of a biochemistry parameter may be graphed against time, thus providing a simple, visual representation of the progression of a disease process or therapeutic regime.

Finally, a discharge summary is a hand-written review of the animal patient's problems and therapy, intended for the owner to take away. It outlines the problems identified during the consultation, the details of the medication prescribed and any other management details about which the owner should be aware (Saidla, 1978; Saidla, 1983; Stogdale, 1984). This aspect of the POMR is an excellent resource in terms of client education, and furthermore, it ensures that appropriate continued patient care will be undertaken (Saidla, 1976; Thrusfield, 1983b).

The POMR offers a number of advantages. The medical record is well organised and structured. The thorough approach to the record demands that a clinician adopt a logical and thorough approach to each patient, ultimately improving individual animal

care and welfare. When an animal patient returns for a revisit, then the clinician can readily review the animal's medical history on the problem list sheet, thus using the consultation time more efficiently. The discharge summary produced for each client is very important with respect to client understanding of the patient problem and continued care for the patient. It is thought that the client will appreciate the effort which the veterinarian has invested in their pet, and may be more likely to return to that veterinary practice. The POMR promotes the maintenance of complete, comprehensive, consistent medical records which is not only important for individual animal welfare, it facilitates epidemiological studies.

Although the POMR promotes the maintenance of comprehensive records, the records can be very time-consuming to complete in a busy practice. Saidla (1983) indicated that within the first component of the POMR alone, a comprehensive defined database may require over 40 minutes to complete. Such time demands on a practising veterinarian may prohibit the use of the system in general practice. However, not all animal visits must be documented in such detail, for example nail trimming may be entered as problem only. Some practices attracted by the POMR system, but unable practically to apply it, have adapted it to suit the needs of a busy practice by adopting a simplified version based on SOAP (Willen, 1976). The system requires a large area for storage of the files, which may consist of a large number of sheets within an envelope or folder (Thrusfield, 1983b). As with the other types of paper-based data storage systems discussed, there is no form of back up, so loss of records due to carelessness or misfiling is a possibility. Importantly, despite the ability of the system to generate important and comprehensive data, there is no means of searching the files, thus limiting the use of the system for research purposes.

2.3.6 Computer

Computers offer an efficient means of storing, analysing and retrieving data (Sard, 1981c; Thrusfield, 1985). The computer was introduced to veterinary practice in the 1970s (Farber, 1986). Originally it was employed as an administrative aid, used primarily for business accounts (Farber, 1986; Miller, 1996), but it became apparent that it would be a useful tool applied to many aspects of practice management, including medical records, stock recording and client credit (Sard, 1981b).

When computerisation was first introduced to veterinary practice, the hardware and software systems available were in their infancy (Sard, 1981a). In the past two decades enormous progress has been made in the field of information technology (Horton, 1995; Miller and Shiffman, 1995). This, coupled with a growing appreciation for the value of information technology in the medical domain, has led to an array of software packages designed for the veterinary user (Stone and Thrusfield, 1989). There are now a number of commercial packages designed for veterinary practice, aimed towards many aspects of management, (examples include VETAID PTY, 1995; Advanced Veterinary Systems, 1996; Animal Services Information Management, 1996; Britton's Wise Computers, 1996; DVM Manager, 1996; Henry Schein Veterinary Products and Services, 1996; Veterinary Software Publishing Inc., 1996; VETSONE Software, 1996; Visionarian System Website, 1996). The extent of computerisation within a practice or hospital can range from one personal computer with basic accounting capabilities (Miller, 1996), to a complex network of relational databases, able to deal with medical records, laboratory data, pharmaceutical stock, and accounting (Thrusfield and Hinxman, 1981; Stone and Thrusfield, 1989). An Electronic Medical Record Survey of North American Veterinary Colleges (1995) revealed that most veterinary hospitals employ comprehensive computing systems, and, often, in such institutes the computerised system which operates is one unique to the institute rather than a proprietary commercial package. A framework of databases is established, perhaps by an independent programming company, and later customised to meet the needs of the institute.

The electronic medical record has developed significantly in both human and veterinary medicine over the last decade (Talbot and Mills, 1994). However, the ideal structure for the electronic medical record, such that adequate details may be stored, but that is not overly time-consuming to complete has not yet been derived (Lussier and Côté, 1995).

2.4 COMPUTERISED MEDICAL RECORD SYSTEMS

2.4.1 Input considerations

The means of entering data to a computerised medical record system is of paramount importance to the future success of the system (Sard, 1981b). If the input is inadequate, then it follows that any output will also be inadequate, jeopardising the potential value of

the system (Beard, 1992). The key issues which must be addressed before satisfactory data input can be ensured include, broadly, what is to be input; how it is to be input; by whom it is to be input; and where it is to be input.

2.4.1.1 Data input

Which data are input currently varies from institute to institute (Electronic Medical Record Survey of North American Veterinary Colleges, 1995). However, the move towards creating the standard veterinary electronic medical record continues (Safran *et al.*, 1995; Boschert, 1996; Boschert, 1997). There are two main considerations which may dictate the details currently stored in any institute. The first is concerned with the patient on an individual level, and the second is concerned with the more long-term goal of epidemiological population studies. The latter may demand more comprehensive record maintenance which, although time-consuming, will allow more detailed epidemiological studies to be performed in the future (Thrusfield, 1983a; Thrusfield, 1983b).

2.4.1.2 Methods of inputting data

The options available with respect to how information may be input are increasing as computer technology itself develops. Physical means of data entry may be by keyboard (Thrusfield, 1985). This entry method, however, may yield mistakes through typographical errors and therefore requires keyboard skills. More recently, "pen-based" methods of medical record recording have been introduced to the human medical domain (Miller and Shiffman, 1995; Poljak *et al.*, 1995; Worth *et al.*, 1995), and are already in use in some North American Veterinary Colleges (Electronic Medical Record Survey of North American Veterinary Colleges, 1995). These systems are of clipboard appearance, but function as portable computers, with all information entered to screens using an "electronic pen". The advantages of the pen-based system include ease of use, portability and lack of intrusiveness in the consulting-room environment. Such advantages may serve to promote record keeping. Input into pen-based systems are menu driven, with specified areas for free text entry. Similar menu systems can be run with keyboard entry systems. Menu systems for data entry promote uniform, comprehensive records, the main disadvantage being the length of time required to develop menus and options that contain most clinical eventualities (Cimino, 1995). However, the alternative, free text entry,

generates non-uniform records, and is consequently more problematic in terms of application of searching mechanisms.

2.4.1.3 Requirement of data coding

Data may be entered in coded format in order to enhance the storage efficiency of the computerised system. Data coding involves representation of medical record details, such as animal breed, gender, clinical signs and diagnosis as defined alphabetical or numerical character combinations (White, 1988). The element of coding which has presented the medical field with greatest difficulty is that of diagnosis coding (Hart *et al.*, 1995; Hohnloser and Puerner, 1995). This is most likely to be due to the extremely complex nature of disease processes and diagnosis (Long *et al.*, 1992). Despite the realisation of the advantages of a standard veterinary nomenclature as early as 1959 (Cohen *et al.*, 1959), the quest for an optimum standard veterinary and medical nomenclature continues (McDonald, 1995). The Electronic Medical Record Survey of North American Veterinary Colleges (1995) revealed that SNVDO, Standard Nomenclature of Veterinary Diseases and Operations, was the diagnosis coding system adopted by most colleges, as was the cases in 1980 (White and Vellake, 1980). Interestingly, a comparison of SNDVO and SNOMED, the nomenclature supported by the American Veterinary Medical Association (Boschert, 1997), undertaken by Klimczak *et al.* (1995), concluded that SNOMED was "a more complete and richer vocabulary than SNVDO". SNOMED has a hierarchical structure which Talbot and Mills (1994) claim is suited to the problem oriented medical record system, facilitating the coding of problems to the level at which they may be confirmed, for example, a digestive problem may be coded simply as such, or may include further "levels" of detail, to indicate intussusception of the colon. If all veterinary institutes and practices were to agree on adopting one coding system, for example SNOMED, then the amalgamation of many databases could be facilitated, offering wide-ranging epidemiological study opportunities.

2.4.1.4 Personnel responsible for data input

By whom the data are entered is a decision which may affect the efficiency and accuracy of the computerised medical record system. Data may be input by the clinician. Although this helps to ensure validity of data entry, a busy clinician must prioritise, and data entry may be regarded as unimportant (Pollari *et al.*, 1996). Data entry may be undertaken by

nursing staff, who could input details initially recorded by the veterinarian in a paper record. Similarly, data could be entered by reception staff or technical staff, a system in evidence at Ontario Veterinary College and at the Small Animal Teaching Unit at the Royal Dick School of Veterinary Studies (Stone and Thrusfield, 1989; Pollari *et al.*, 1996). This is advantageous with respect to these staff often being more comfortable with computer technology, but, if inadequately supervised, may result in the input of invalid results, through misunderstanding of veterinarians' notes. However, from the evaluation of the computerised medical records undertaken by Pollari *et al.* (1996), it may be concluded that if a clear and complete case summary sheet is provided by a veterinarian, then the computerised record will also be accurately completed.

2.4.1.5 Location of data input screens

The location where the data are entered is of importance, particularly when installing a new system. Entering data in the consulting room has a number of advantages in that it facilitates mental recall of a case; may allow access to all further test results; and promotes completion and update of the computerised medical record. However, the introduction of computerised systems to the consulting room may be viewed as intrusive by the client. In this situation, a pen-based approach may be more appropriate because it has been shown to be less intrusive in similar environments within human medicine (Poljak *et al.*, 1995). Alternatively, data may be input in reception or clinical records areas, which may be deemed more appropriate by the client. In the future, however, computer technology is likely to be present in aspects of most professions and may ultimately even be expected by the client.

2.4.2 Assessment

Computerisation of the veterinary medical record system offers a number of advantages. It improves overall practice or hospital management efficiency in a number of ways (Rude, 1986). There is no requirement for filing and refiling of medical records since the appropriate record may be viewed on the computer screen when required, a process which takes seconds rather than minutes. It is impossible to misfile a record, as they are saved and retrieved automatically by the computer, a process transparent to the user (Sard, 1981a). If the computerised system is multi-user, then the medical record for any client may be accessed by a number of clinical staff at any one time. As long as an

adequate back-up system operates, the likelihood of any record ever becoming lost is negligible. These features all markedly improve the administrative aspect of medical record maintenance.

Although the specific capabilities of any computerised medical record system vary depending on the individual set-up, generally, it is possible to perform searches of computerised medical records. This improves the potential ability of a computerised medical record system to act as a research tool, especially for epidemiological studies (Sard, 1981b; Kock *et al.*, 1989). Computer technology allows vast amounts of information to be stored within limited physical space (Miller, 1996). Using such technology, computerised systems can maintain many archival records. For epidemiological studies to have sufficient statistical power, large numbers of cases are often required, and thus the ability to store and query large amounts of clinical data is advantageous for veterinary research (Martin *et al.*, 1987). It may ultimately be possible to run computerised medical record systems which are compatible with data analysis packages, facilitating epidemiological research.

However, as with each of the medical record systems described, there are a number of disadvantages currently associated with computerised medical record systems. Installation and maintenance is expensive in comparison to most paper methods. Whether a computerised record system was to be largely maintained and updated by a select few, or would involve most personnel, training to use the system would be required (Sard, 1981b). Most importantly, as with any electrically based equipment, unforeseen power-cuts may result in temporary interruption of the service, and adequate back-up facilities are therefore vital (Millman, 1996).

Despite these few disadvantages, the computerised medical record system is undoubtedly the medical record system for the future. It may be suggested that in a number of years to come, all medical and veterinary medical record systems will be completely computerised. Currently, however, most computerised systems run in conjunction with paper records (Electronic Medical Record Survey of North American Veterinary Colleges, 1995). This may be for a number of reasons, including that many veterinary practitioners are wary of computer technology in the practice (Miller, 1996) and demand paper back-up; if an efficient means of entering data is unavailable, then computerised systems may be more time-consuming on a day to day basis; and the

electronic medical record is not yet considered a legal document (Millman *et al.*, 1996).

2.5 POTENTIAL APPLICATIONS OF STORED DATA

Primarily, medical records are stored in order to maintain an account of an animal's health status (Thrusfield and Hinxman, 1981). However, computerised medical record systems offer a number of advantages to the functioning of a practice through an array of different output capabilities. Pharmacological labels may be printed automatically to contain the legally required information; vaccination reminder lists may be generated automatically; and clients within specified demographic areas may be readily identified and informed of any local disease outbreaks. Most importantly, in terms of research, the maintenance of computerised medical records may facilitate the conduction of valuable epidemiological studies. By way of such epidemiological studies, further understanding of disease processes, identification of populations at risk and ultimately improvement in animal care welfare may be gained.

At the University of Glasgow Veterinary School, a number of different data recording systems have been implemented over the years. In Chapter 3, a brief overview of GUVS is followed by a description of the data recording systems, focusing on the computerised relational database system used within this thesis.

CHAPTER III

UNIVERSITY OF GLASGOW VETERINARY SCHOOL HOSPITAL DATA RECORDING SYSTEMS

CHAPTER III

UNIVERSITY OF GLASGOW VETERINARY SCHOOL HOSPITAL DATA RECORDING SYSTEMS

"Computers are paradoxical creatures. At once powerful and impotent; amazingly brilliant and incredibly stupid; fanatically obedient and terribly demanding"

Fredric Stevens (1986)

3.1 UNIVERSITY OF GLASGOW VETERINARY SCHOOL HOSPITAL - AN OVERVIEW

Glasgow Veterinary College was founded in 1862, and incorporated into the University of Glasgow in 1949. Initially Veterinary Medicine was part of the Faculty of Medicine, but in 1968 the independent Faculty of Veterinary Medicine was formed. The University of Glasgow Veterinary School (GUVS) now functions as a veterinary referral unit and a teaching and research institute. It is responsible for the referral care of a wide variety of species, but most usually dogs, cats, horses, cattle and sheep. For most of the species, clinical cases are referred from general veterinary practices in the surrounding geographical area. GUVS is one of only two such institutes in Scotland, so some animal patients must travel long distances.

Within the clinical domain, the species disciplines are separated into three basic groups, namely, small animal, farm animal and equine. Increasingly over the years, as has been reflected more widely in general veterinary practice, the three disciplines have become more separate, and now function as individual divisions. Within the small animal division, there are approximately 12 members of clinical teaching staff and 12 clinical scholars; within the farm animal division, there are 5 members of clinical teaching staff and 3 clinical scholars; within the equine division, there are 4 members of clinical teaching staff and 4 clinical scholars. Currently, the small animal clinic generates on average 167 cases per month, the Equine Weipers Hospital generates around 27 cases per month, and approximately 22 new large farm animal cases are investigated per month. Each animal which presents to the hospital undergoes comprehensive historical and clinical examination, further ancillary clinical testing, if required, and ultimately

therapy and follow-up investigations. From this brief overview of the clinical aspects of the hospital, it may be appreciated that large volumes of data are generated over short time periods. It is, therefore, of the utmost importance that a reliable data recording system is in operation.

3.2 MEDICAL RECORD STORAGE AT GUVS

Even before an animal is examined by a clinician at the Veterinary School, it is required that various data are recorded. Such data include details of the animal - age, sex, breed; details of the owner - name, address, contact; and, similarly, details of the referring veterinarian. Figure 3-1 displays the typical route which may be followed by an animal investigated at GUVS, and highlights different data which may be generated at each stage. For the efficient running of the hospital, it is essential that all relevant information is methodically stored, and may be readily retrieved. The University of Glasgow Veterinary School hospital records have been maintained since the 1950's, over a period spanning more than 40 years. Throughout this time, the system has undergone changes as technological advances have improved data recording systems. From original maintenance of paper records alone, GUVS has progressed to a comprehensive computerised relational database system.

3.2.1 Hard/Paper records

In earlier days, records were maintained on paper only. The records were initially unstructured, and contained only minimum information. However, as different clinicians have worked at GUVS and as the amount of information recorded for any one animal has increased, discussions as to the ideal structure of the paper record have continued to progress. A *pro forma* style paper record has been adopted, with space for free text entry, where necessary. Separate sheets may be used to record history, and clinical examination details. The sheets are kept together in brown envelopes, labelled with the animal's hospital number. If further tests are performed, such as clinical biochemistry or microbiological testing, then the appropriate report sheets are inserted in the individual animal's record envelope.

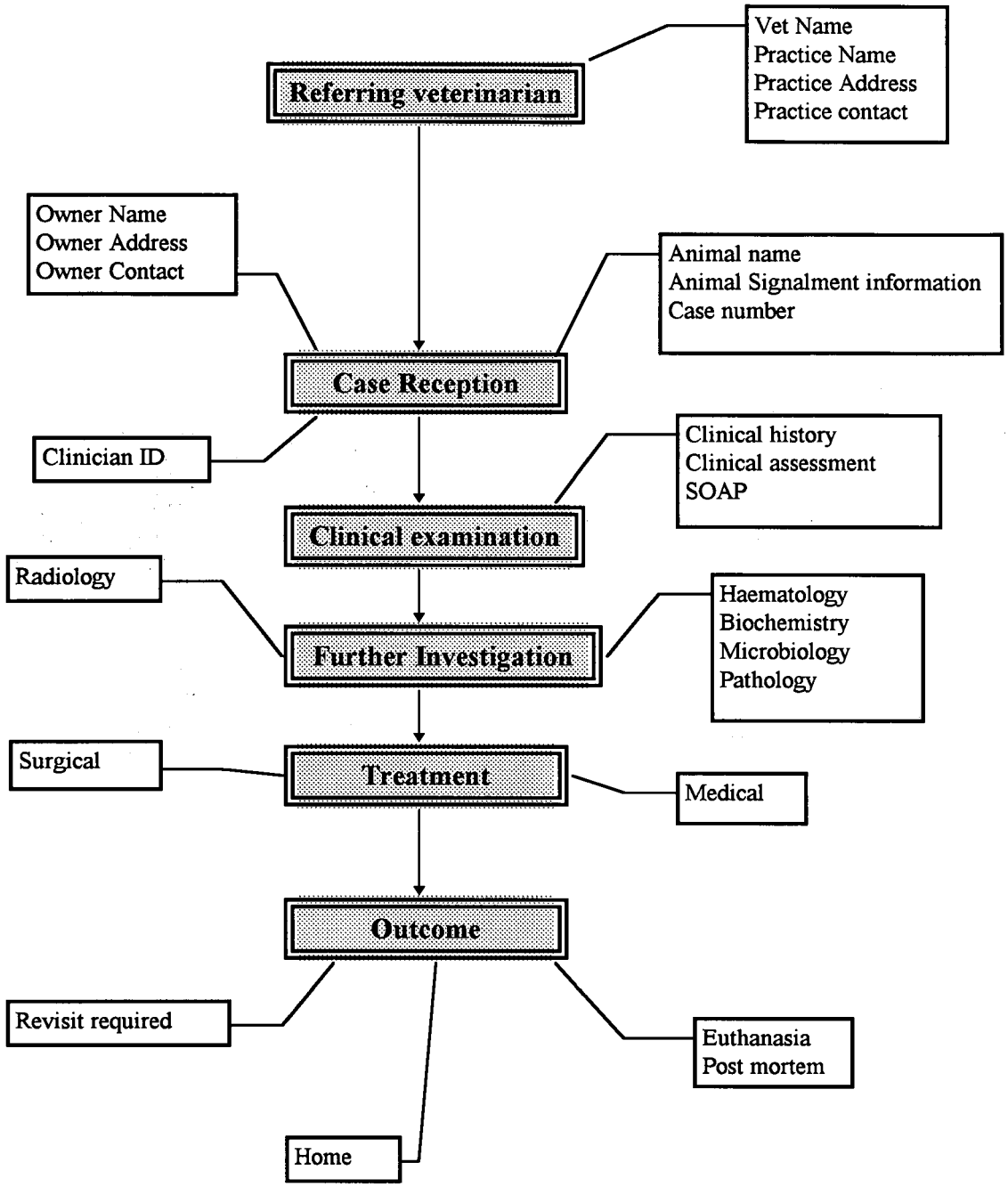


Figure 3-1 Representation of various investigative stages through which animals proceed, and type of data stored at each stage, during hospitalisation at University of Glasgow Veterinary School.

Until the last few years, the format for paper records has been largely the same for different species. However, recent developments within the Department of Veterinary Clinical Studies, separating species specific personnel into divisions, have encouraged the development of different paper record structures for different species.

All medical record envelopes are stored in numerical order within filing cabinets in the clinical records office. Due to space restrictions, only records belonging to animals which have been seen within the last 24 months, approximately, are kept in the clinical records office. Records from animals seen prior to this time, are maintained in a separate storage area. Access to the paper medical records is controlled by the clinical records office personnel. All persons removing medical records from the office are required to complete a log indicating their possession of a medical record, and similarly, the return of the record. Given that only one hard copy of any medical record exists, this procedure is vital. However, despite such strict enforcements, a large proportion of hard records are known to be missing.

The concept of the paper record system is familiar to all users, veterinarians, nurses, students and receptionists and, equally, clients accept this mode of data recording. The *pro forma* style record is easy to understand and to complete, its use requiring little, if any, training. The paper record system is a relatively inexpensive means of maintaining comprehensive, and up-to-date medical records. The brown envelope filing system has been successful within the Veterinary School environment, the envelopes proving sufficiently robust to last several years of filing and refiling.

One of the major problems associated with the paper record system at GUVS, is the fact that there is only one copy of the record. Often, different people may wish to refer to a record at the same time, yet this is impossible. Further, the maintenance of separate sheets within the one envelope has often resulted in one person removing only the sheet in which they are interested, for example a pathology report, and thus an incomplete medical record remains. These factors, together with legibility issues, inability to readily perform searches of historical data, lack of any back-up facility and storage space requirements, demanded that different medical record systems must supersede the paper medical record, or, at least, be run in conjunction in conjunction with the existing system.

The problems associated with back-up and storage space facilities were addressed first by the introduction of a Microfiche system, and more recently by the Canon (Canofile 250) System.

3.2.2 Microfiche

Microfiche offered a means of storing reasonably large amounts of data in a compact form. These films were maintained in dark storage areas, and when information about past cases was required the film was examined using a dedicated viewer. Records dated from 1955 to 1989 continue to be stored in this way.

3.2.3 Canon System

The Canon System allows an exact copy of an animal's entire paper record to be maintained in an electronic format, such that if the paper record is destroyed, a permanent record of all details will be maintained for any possible future reference. The paper records are manually scanned into the Canon System. The Canon file basically provides a visual image of the paper record, and has only very limited search facilities. The concept of maintenance of records on the Canon System is admirable and with many advantages; however, the quality of many of the images is such that the records are effectively useless.

3.2.4 Computerisation

Although a Termatrex system introduced to GUVS around 1970, based on a model from the University of Pennsylvania, had allowed basic search facilities, introduction of computerisation to the veterinary hospital revolutionised record storage and retrieval. As detailed in 1.2, maintenance of computerised records had been instituted in individual departments, namely biochemistry and pathology, for a number of years before funding was provided to establish a fully integrated system (Gettinby *et al.*, 1991). Largely due to the foresight of a team of pathologists and clinicians, the fully computerised system of data recording was implemented at GUVS in 1988 (Gettinby *et al.*, 1991). The DataFlex (Data Access Corporation, Miami, Florida, USA) relational database system was comprised of a number of networked databases capable of storing signalment, clinical, biochemical, haematological, microbiological and pathological information (Hospital

Computer System User Guide, 1988). The electronic medical record system was run in conjunction with the paper record system. The practice continues today.

3.3 THE GUVS HOSPITAL COMPUTERISED MEDICAL RECORD SYSTEM

Introduction of the computerised medical record system to GUVS was a pioneering action, and predated the development of suitable commercial packages. It was therefore necessary to invest in a bespoke computerised database system which was subsequently customised for the purposes of the veterinary hospital. A number of factors were involved in the selection of the optimum system for the veterinary school to ensure fulfilment of various requirements, such as provision of sufficient disc space for maintenance of comprehensive records, ability to input and retrieve data easily, ability to customise the facility to search the database, and financial considerations.

3.3.1 Hardware

The GUVS Hospital computer system consisted of a number of networked clusters, each of which was supplied by a central microcomputer (Hospital Computer System User Guide, 1988). There were six clusters in total - medicine, routine pathology, biochemistry, experimental pathology, canine infectious disease research unit and feline virus unit (Figure 3-2). The majority of the GUVS medical records were maintained in the medicine, biochemistry and routine pathology clusters.

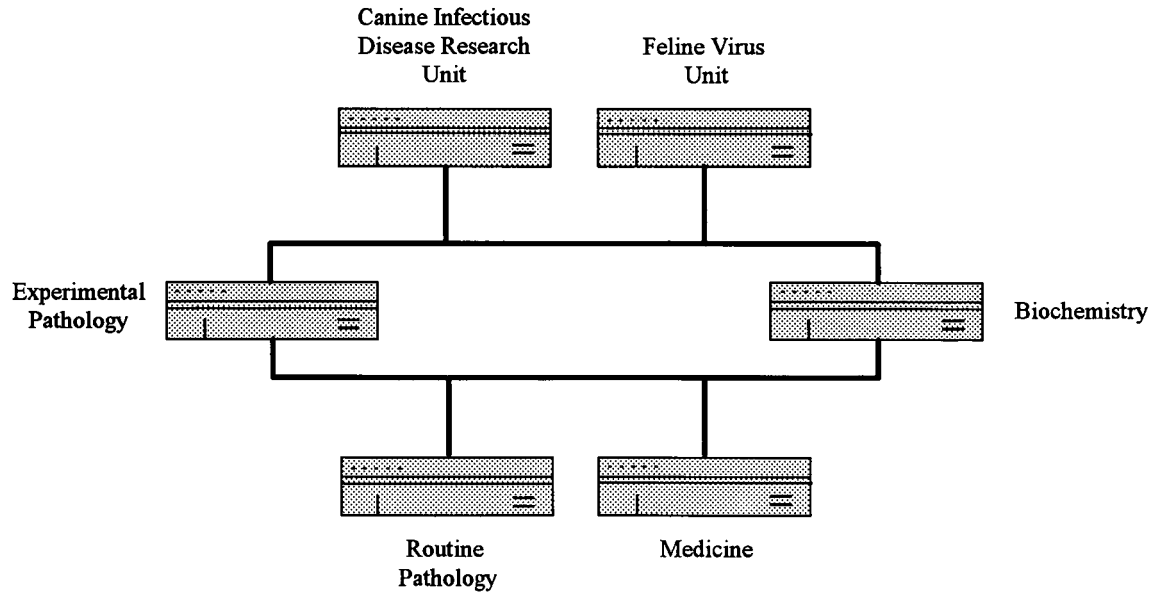


Figure 3-2 Representation of network of microcomputers which formed the basis for GUVS Hospital database. Most of the data in the medical record database were entered and retrieved from the Routine Pathology, Medicine and Biochemistry servers.

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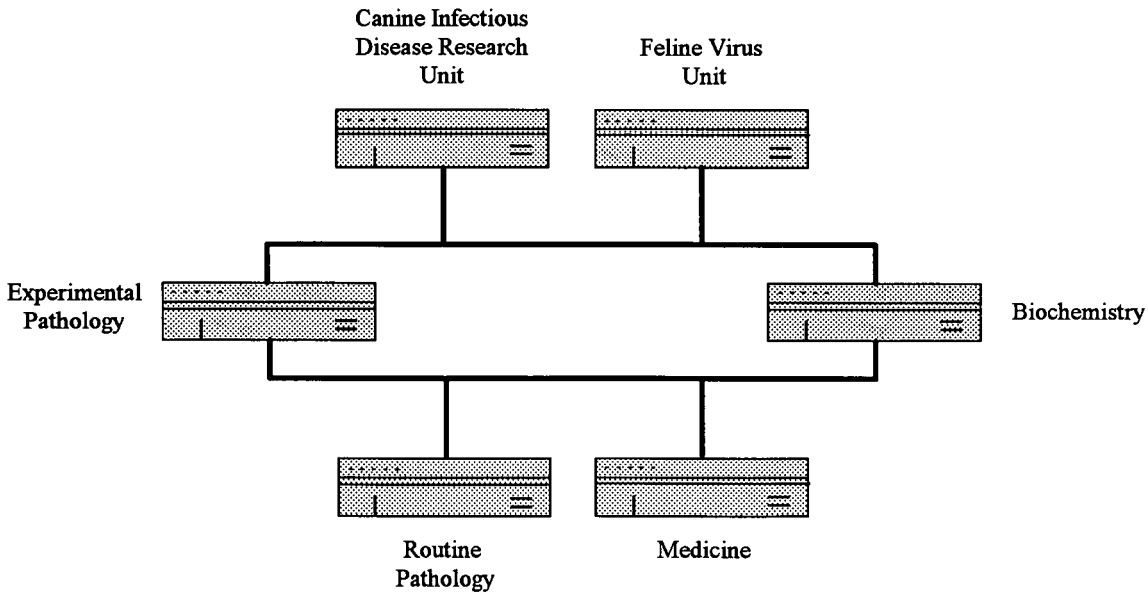


Figure 3-2 Representation of network of microcomputers which formed the basis for GUVS Hospital database. Most of the data in the medical record database were entered and retrieved from the Routine Pathology, Medicine and Biochemistry servers.

Each cluster comprised a microcomputer supporting several visual display units (VDUs) and printers. Each microcomputer had an 80286 or 80386 processor, 1-4MB of memory, a 40 or 80MB hard disk and a 780KB or 1.2MB floppy disk drive, requiring 5.25" disks. The computers chosen were Jarogate Sprite 286 and 386 units - multi-user machines running C-DOS and CCP/M (Hospital Computer System User Guide, 1988). Figure 3-3 depicts the layout of the medicine cluster alone, the central microcomputer serving associated VDUs and printers.

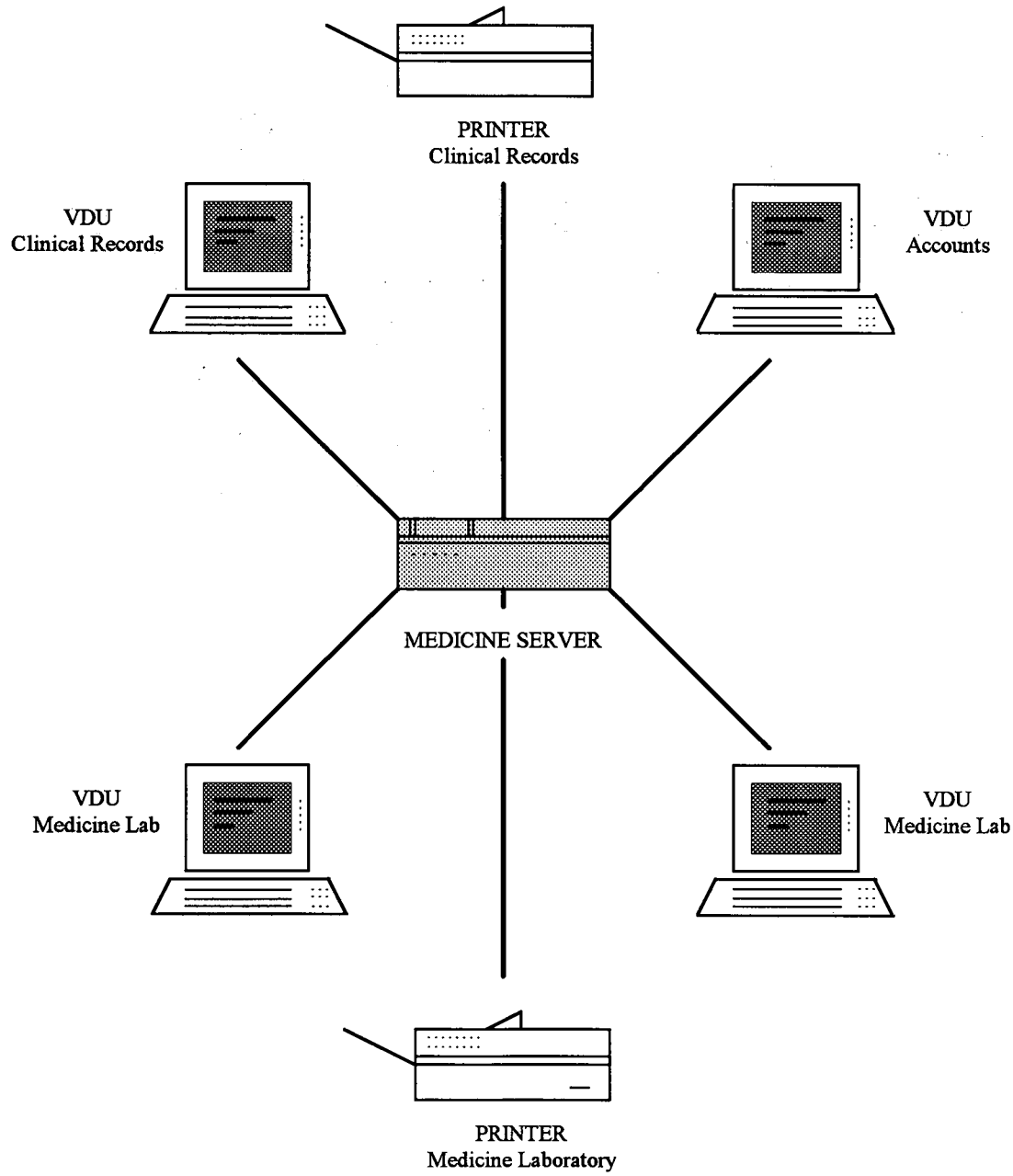


Figure 3-3 Layout of the visual display units and printers which were directly supported by the MEDICINE SERVER. The medicine server was one of six networked servers for the GUVS hospital system.

3.3.2 Software - DataFlex system

The GUVS Hospital database system was developed using DataFlex, a commercially available, multi-user, relational database system. The system had the potential to support up to 250 different data files, each with up to nine indexes. The system was installed and customised for the veterinary school's purposes by an independent company, "Specialist Services (Scotland) Ltd" (Hospital Computer System User Guide, 1988). The multi-user facility of the database could support simultaneous access of the database by up to 15 people at a time. Furthermore, the query language contained within the DataFlex system was advanced and would facilitate future epidemiological investigations.

3.3.3 Back-up

Back-up facilities were provided by a tape deck system, with six tapes. This allowed new information stored on the database to be saved at the end of each day, such that in the event of a serious problem, only information from one day would have to be re-entered to the database system.

3.3.4 Financial implications of computerised system

The introduction of the computerised system was expensive, but expected to allow clinical and receptionist personnel to work in a more time-efficient manner, and ultimately provide cost benefits. From a more indirect perspective, the recording of clinical information would enable future valuable epidemiological studies. Such studies are often productive, particularly when large comprehensive databases are available to the researcher, and are likely to promote publications and encourage external funding for the University. The purchase price of the hardware and accompanying software system in 1988 was approximately £80,000.

Almost ten years on from the installation of the integrated hospital system, the computerised data collected have proved invaluable to the Veterinary School, and the system is currently being upgraded. Interestingly, the value of data has been realised in many facets of life, not just in the medical sciences, but throughout other academic and industrial institutions. Recent increases in computerisation in the veterinary practice domain reflect this, and confirm that the GUVS hospital was installed with foresight.

3.4 COMPUTERISED MEDICAL RECORDS

The introduction of the computerised system demanded that the structure of an electronic medical record be established. It must also be appreciated, that computerisation was to run in conjunction with the paper record system already in operation, and not to replace it. First, the types of data which were to be recorded were identified; and subsequently, a file structure which would ensure efficient data storage and extraction was created. This involved the development of various coding systems to prevent unnecessary repetition within the database.

3.4.1 Type of data stored

The types of data to be maintained within the veterinary hospital database were many and varied, as reflected by Figure 3-1. All information of import to the individual animal had to be recorded in electronic format. This included not only details pertaining to the identification of the animal, its owner and referring veterinarian, but also to the GUVS clinician under whose care the animal was, clinical examinations which it would undergo, further tests, outcome and revisits. Thus from the animal's name, to its panel of clinical biochemistry results on a certain date, scope for recording and retrieving was required.

3.4.2 File structure

The central core of the system consists of the Central Animal File (Hospital Computer System User Guide, 1988). When a patient first enters the hospital system it is allocated a hospital number which remains the same throughout any subsequent visits to GUVS. This numbering system had operated within the hard record system, and the decision when the computerised relational database system was established was to maintain consistency in this regard. Hospital numbers are allocated sequentially, independent of species. The hospital number forms the main identifying factor in the Central Animal File, within which there are a number of fields containing information on animal identification - name, species, breed, date of birth, sex, whether alive or not; referring veterinarian identification; owner identification; GUVS staff identification; date the animal was first seen; date the animal was last seen; and the number of haematology tests, biopsies, necropsies, biochemistry panels, diagnoses, case summaries and bacteriology examinations it has undergone. Thus the Central Animal File basically contains summary

information on any one animal stored within the database. The details are in fact maintained within separate files, to which the Central Animal File refers.

The GUVS hospital database essentially consists of the Central Animal File and two additional types of file, "upper" and "lower" (Figure 3-4) (Hospital Computer System User Guide, 1988). The upper files, entitled "specbred", "owner", "vet" and "staff1", contain details of the species and breed of the animal, details of the owner, the referring veterinarian, and the GUVS clinician, respectively. Maintenance of the information in this manner allows, for example, different animals to point to the same referring veterinarian thus preventing repetition and saving disk space. This may be achieved because in the "vet" upper file, a unique identifying number is allocated to each veterinarian, and it is only this number which is stored in the Central Animal File. This pointer system applies to the other upper files, i.e. each owner, each staff member, and all species and breeds are given unique identifying numbers, the details of which are held in the upper files.

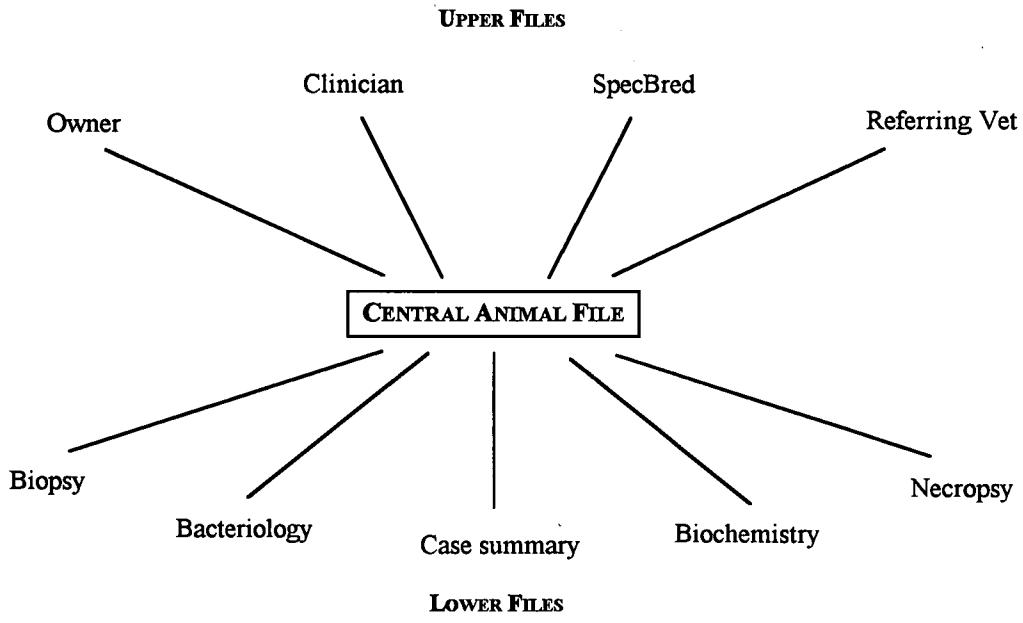


Figure 3-4 Representation of the layout of the files which comprise the GUVS Hospital database system. The Central Animal File lies at the core of the system, with pointers to the upper and lower files.

The lower files hold different types of clinical and paraclinical data recorded for each animal. Entitled "biopsy", "bact", "summary", "biochem" and "necropsy", they contain details of biopsy results, bacteriology results, case summary details, biochemistry results and necropsy reports respectively. A file containing each animal's haematology is a more

recent addition to these lower files, and is entitled "haem". Each record within a lower file has a two part unique identifying number. The first part is the animal's hospital number, and the second relates to the number of, for example, biochemistry, tests carried out for that animal.

3.4.3 Coding

As hinted in the explanation of the file structure of GUVS hospital database (3.4.2), the requirement for several coding systems was of utmost importance to ensure both consistency of entry and efficient use of disk space. Coding systems are employed both within the upper and lower files. For example, Table 3-1 outlines part of the coding system adopted within the "specbred" file. A small selection of breeds from four different species, namely, cats, cattle, dogs and horses, have been chosen to explain the coding system. In total, 96 different species, within which there are numerous breed specifications, are represented in the coding system. Each species is allocated a code, for example cat = 2; within the species, two breed categories allow for detailed recognition. For example, if the cat were Siamese it would be represented by "breed1 code =21", and if it was known to be chocolate point, it may further represented by "breed2 code = 1". This system allows detailed identification to be stored for each animal. A similar system operates for the identification of clinical staff within GUVS hospital (Table 3-2).

The use of coding has been encouraged within some of the lower files to promote consistency of entries, of particular importance for retrospective studies. An example of this is evidenced within the biopsy file, where the field "site" is a number which refers to one of approximately 50 possible sites which best identifies the location of a lesion. For example, "site = 29", refers to "bones"; and "site = 13", refers to upper respiratory.

Staff Ref	Key	Name	Department
1	MM	Max Murray	Veterinary Clinical Studies
2	ASN	Andrew Nash	Internal Medicine
3	NAMCE	Neil McEwan	Dermatology
4	IES	Ian Selman	Medicine

Table 3-2 Example of the coding system employed within the GUVS hospital database system to identify members of clinical staff.

Species	Breed1 description	Breed2 description	Species code	Breed1 code	Breed2 code
Cat	DLH*		2	7	0
Cat	DSH†		2	8	0
Cat	Siamese	Chocolate point	2	21	1
Cat	Siamese	Cream point	2	21	2
Cattle	Aberdeen Angus		3	1	0
Cattle	Aberdeen Angus	X	3	1	99
Cattle	Fresian		3	10	0
Cattle	Fresian	X	3	10	99
Dog	Boxer		4	12	0
Dog	Boxer	X	4	12	99
Dog	Collie	Bearded	4	20	1
Dog	Terrier	Jack Russell	4	92	16
Horse	Hunter		7	17	0
Horse	Shetland pony		7	26	0
Horse	Thoroughbred	X	7	30	99
Horse	Welsh Cob	X	7	34	99

*DLH - domestic longhair; †DSH - domestic shorthair.

Table 3-1 Example of some of the more common species and breed codes which are used for data storage in the "specbred" file of the University of Glasgow Veterinary School Hospital database. There is a total of 96 species which have been coded, within which many different breed details are possible.

3.4.4 Data input

For the maintenance of a comprehensive data recording system to be worthwhile, it is vital that all relevant data are input and regularly updated. As outlined in 2.4.1, careful consideration must be given to the logistics of data input, that is, by whom, how, when and where. Table 3-3 summarises the main categories of data input, the location of the consul at which they are usually input, and the person responsible in cases where the uploading is not automatic. Animal details, name, age, breed, and so on, are the responsibility of the receptionist. Input screens prompt the user for this, and other, vital information such as owner's name and address, referring veterinarian and staff references. This information must be stored within the database before the paper record for an animal is created, and ensures that the most basic information pertaining to each animal is recorded.

Entry of the clinical aspects of a case is the responsibility of the clinician in charge. There is no scope for entry of information to the computer at the time of consultation, because there are no consuls within the consulting room. This demands that the clinician must up-date the computerised record some time later. This aspect, coupled with the fact that many of the clinicians are not comfortable with using the computer system, has resulted in many aspects of the clinical data being missing from the database. Queries of the database reveal that certain clinicians always update the electronic records, while others almost never input information. However, in more recent years, the value of the comprehensive database has been realised and clinical staff have been more actively encouraged to up-date the computerised records.

Table 3-3 indicates that some of the laboratory data may be automatically uploaded, for example the clinical biochemistry data. This is enabled by specialist analyser hardware and software compatibility with the hospital system. For the clinical biochemistry data, the results of tests are presented as continuous data, and manual input would incur many transcription errors. The automatic nature of this aspect of the database is therefore not only time efficient, but also yields a more accurate database. Despite the advantages of automatic uploading, recent installation of a new biochemistry analyser negated the ability to continue this practice, as outlined in 5.3.2.1. However, efforts are currently underway to revise the situation.

Data	Location entered	Automatic/ Manual input	Person responsible
Animal ID	Clinical Records Office	Manual	Receptionist
Owner ID	Clinical Records Office	Manual	Receptionist
Referring vet ID	Clinical Records Office	Manual	Receptionist
Staff ID	Clinical Records Office	Manual	Receptionist
Case summary	Medicine lab	Manual	Vet
Biochemistry	Biochemistry lab	Automatic	
Bacteriology	Bacteriology lab	Manual	Bacteriologist
Pathology	Pathology lab	Manual	Pathologist

Table 3-3 Breakdown of the type of data stored in the GUVS computerised system, location of consul where data input, method of data input, and person responsible for updating records.

3.4.5 Data extraction

Most simple and efficient data extraction from the GUVS hospital system is achieved through the built-in query language. Through this system, all the files containing details of cases seen at GUVS can be interrogated. Queries can be run on the upper files, the Central Animal File and the lower files. The central animal file is special in that it provides pointers to both the upper and lower files, as detailed in 3.4.2. The distinction of the upper and lower files at this stage must be understood to make best use of the query facility. Queries of the upper files can be undertaken, but this only provides access to the field information within those files. More commonly undertaken are interrogations of the lower files, from which information within the Central Animal File, and the upper files may also be accessed. However, two lower files may not be interrogated simultaneously, i.e. the clinical diagnoses, maintained within the "case summary file", may not be extracted at the same time as clinical biochemistry results, maintained in the "biochemistry file". Means of conducting such specialised interrogations are possible, but demand the use of customised programs which can be compiled within the DataFlex system.

When employing the query facility within the hospital system, the user is led through a series of screens at which various selections must be made in order to identify which file is to be interrogated, which fields held within that file are required for the

output requirements, what field information is to be output, and how the data are to be output. Figure 3-5 outlines five key screen selections which are required, using an example of searching within the biochemistry file, "biochem", for the hospital numbers, total protein and globulin results for horses only. First, the file to be interrogated must be selected. In this example, the lower file "biochem" must be selected because it contains the biochemistry results. Second, field selection criteria may be stipulated, if necessary. To interrogate the database with respect to horses only, it is at this stage that "species = 7" would be selected. Third, the order in which the data are to be output must be instructed, and "hosp_no" is usually the most convenient and logical. Fourth, the fields containing the data to be output must be selected. Choosing "hosp_no", "totprot" and "glob" fulfil the requirements of the original query. Finally, instructions as to "where" the data are to be printed are required. Data may be printed to the screen, but more usefully may be printed to an output file on the hard drive.

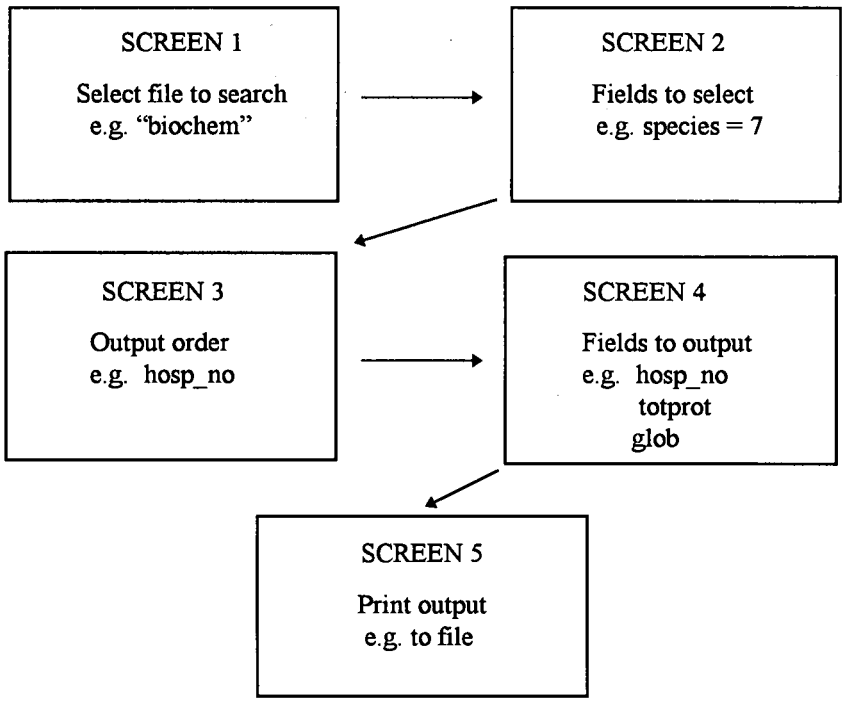


Figure 3-5 Representation of query screens within GUVS hospital database system at which user must make selections, specifying file to interrogate, fields by which the data are to be selected, order in which the output data is to be compiled, fields which are to be output, and where the output of the query is to be printed.

If "file" is selected, then further screen prompts with respect to desired filename and file format, such as "comma delimited" or "printable report" ensure that the data will be

readily accessible to the user. Once the output file is stored on the hard disk, it can subsequently be copied from the GUVS hospital system, via floppy disks to any personal computer, where it can be manipulated as the user desires.

3.4.6 Manipulation of extracted data

Having created the output file containing the relevant information in the format stipulated, and copied it from the GUVS hospital system onto a 5.25″ floppy disk, and then on to a standard 3.5″ disk, the most simple method of manipulating the data is to subsequently export the file to a Microsoft Excel 5.0 workbook (Microsoft Corporation). This is best achieved by running Excel, and opening the relevant file from within Excel. The "Text Import Wizard" within versions 5.0 and above of Excel, automatically detect that the selected file is not in Excel format, and the user is prompted to provide information with respect to data type, in particular detailing whether the data are delimited, and, if so, by what character, e.g. commas or tabs. The data are thereafter automatically imported to an Excel spreadsheet within appropriate columns. Continuing the example above, were the output file for the equine biochemistry results query imported to Excel, three columns representing hospital number, total protein results and globulin results would be created. It is then advisable that the file is subsequently saved in Excel format. The file may then be manipulated readily using all spreadsheet functions.

3.5 Recent upgrading of GUVS Hospital system

Since the initiation of the work which has formed the basis for this thesis, the GUVS Hospital database system has been upgraded in some regards. As technology within the veterinary and medical environments has progressed, the need to update the computerised database system has become apparent. Further possible future improvements to the system are outlined in Chapter 9. However, as the hard disk which contained all the data within the fields and files of the database became saturated, and the system frequently malfunctioned and often crashed resulting in the loss of data which had not yet been backed up, the requirement for "emergency" measures to maintain everyday function of the database became obvious.

3.5.1 Transfer of data to server

The main measure instilled was the transfer of all the data from the hospital network to a new server. The files were ported to a Novell Netware Server, maintained on GUVS premises. The system changed from a version of DataFlex which ran on CCP/M to a more recent version running on DOS. The entire server is backed-up to tape cartridges daily. This implementation of the updated system can support wider multi-user access at any one time and has improved time efficiency of using the database.

3.5.2 Networking of staff personal computers

With the advent of the electronic medical record data being maintained on the Novell Netware Server, any networked computer with the appropriate password permissions can be used to access the hospital data. This has resulted in all clinical staff having immediate access to the system from their desk-top computer. Although the query system continues to be operated in DOS, a more simple menu-driven style presides. This is likely to encourage the clinicians to use the database to its full potential, and thereby, promote data entry to the system.

3.6 SUMMARY OF RECORDS WITHIN GUVS HOSPITAL DATABASE

The fully integrated computerised hospital system has been maintained since 1988. Currently stored within the database are details pertaining to almost 25,000 animals. Although the system contains details on almost 100 different species of animals, the majority of the records relate to canine, feline, bovine and equine cases, with dogs appearing approximately five times as often as any other species.

3.6.1 Animals first seen between July 1990 and July 1997

The pattern of referral cases presenting to the Veterinary School in the last seven years is illustrated in Figures 3-6 and 3-7. Unfortunately, although clinical and paraclinical details of a large number of cases first seen between 1988 and 1990 are available on the hospital database, the date when the animal was first seen was not regularly recorded, and thus this field is not reliable for search purposes prior to 1990. Figure 3-6 highlights the disparity between the large number of dogs seen compared to the number of other species presented. However, a distinct pattern in frequency of presentation for dogs is apparent in Figure 3-6, such that in 1992 to 1994, there was a drop in the number of

cases seen in comparison to other years. In Figure 3-7, representing cats, cattle and horses only, a similar trend is depicted. It is interesting to consider the reasons for such a trend, which has now reversed, as a greater number of cases continue to be seen each year. The drop in cases between 1992 and 1994 may reflect the political and economic state of the country at that time which was during a recession. It may also reflect more directly upon GUVS, with respect to which clinicians were employed, or perhaps more importantly not employed at that time. Since October 1996, a hospital director has been in charge of the small animal clinics, and the existence of such a position may promote an increased case-load in future years.

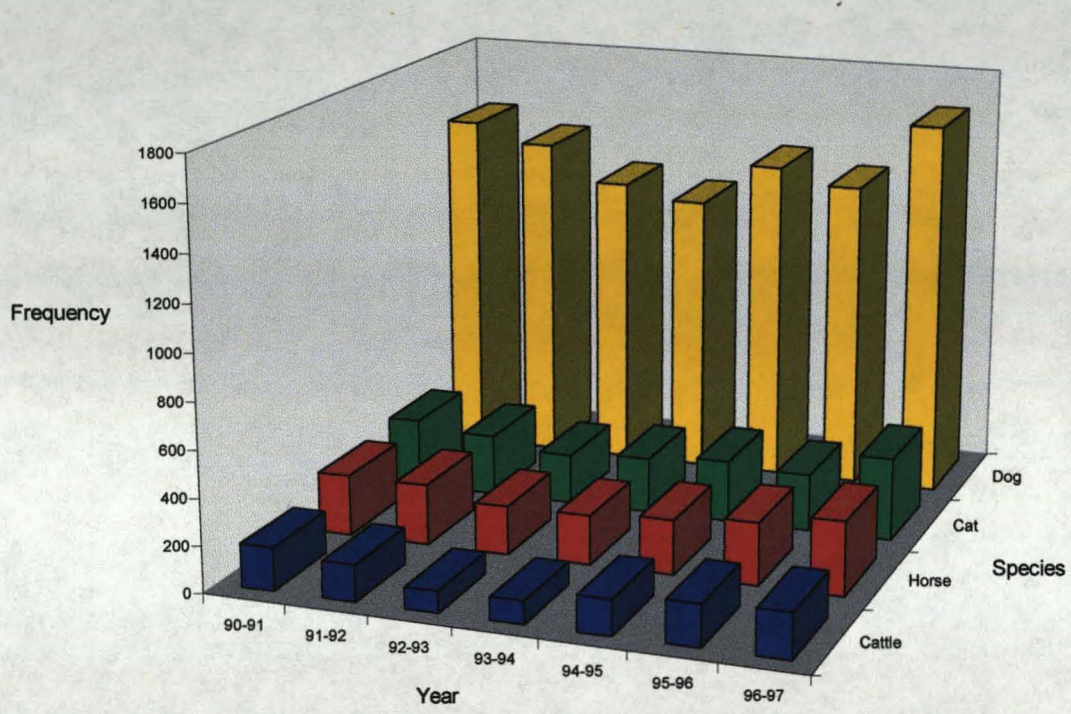


Figure 3-6 Numbers of canine, feline, equine and bovine cases seen at GUVS Hospital between 1990 and 1997.

Figure 3-8 shows a month by month breakdown of canine, feline, equine and bovine cases seen from July 1996 to June 1997. The trend appears to indicate that in August and September, December and March, the number of cases which present to the hospital is reduced. This is most likely a reflection of the University Summer, Christmas and Easter holiday periods.

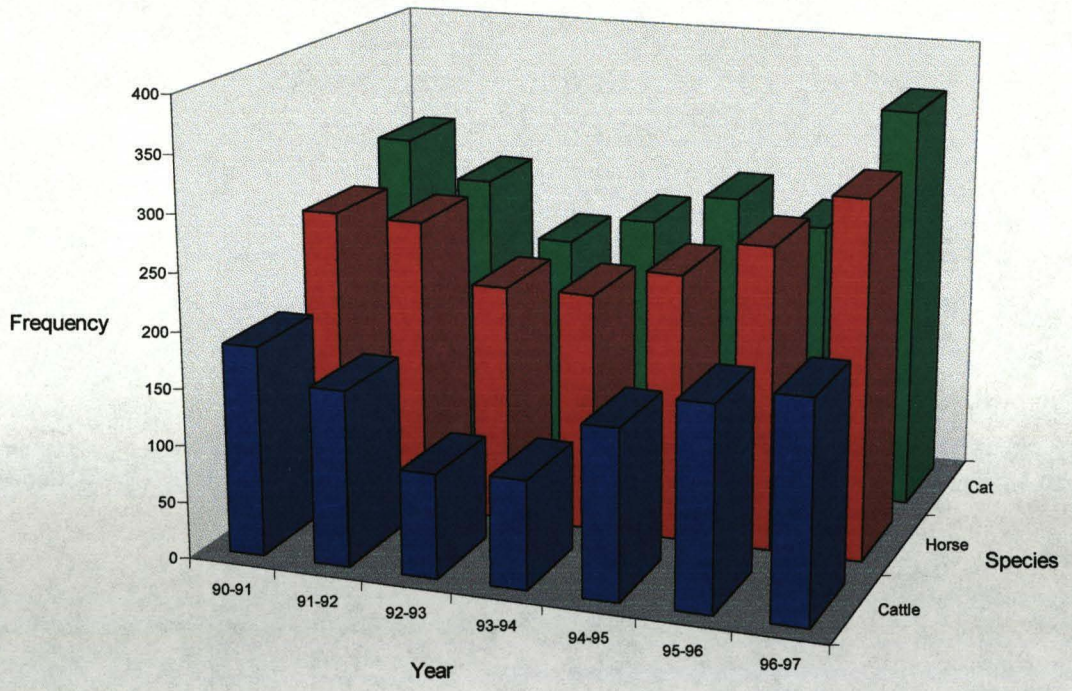


Figure 3-7 Frequency of feline, equine and bovine cases seen at GUVS Hospital between 1990 and 1997.

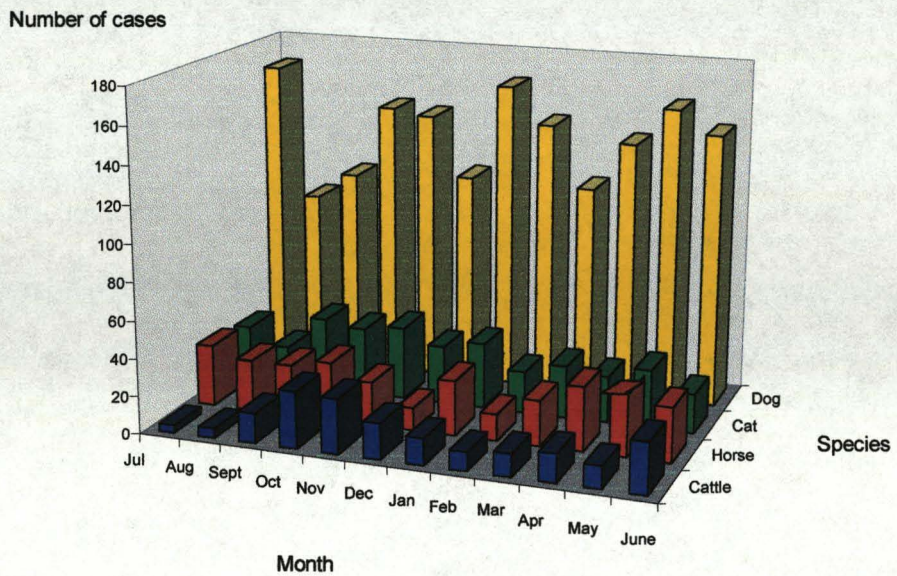


Figure 3-8 Month by month breakdown of frequency of the major species, namely, dogs, cats, horses and cattle, seen at GUVS between July 1996 and June 1997.

3.6.2 Animals with clinical biochemistry testing

Those records of particular importance for this thesis, were the clinical biochemistry results. Interrogation of the GUVS database for this thesis was restricted to equine and bovine cases. As is reflected in Table 3-4 by a summary of the total number of cases of dogs, cats, cattle and horses undertaken in 1995, although the smallest dataset with respect to clinical biochemistry results is for the horse, it has the highest proportion of clinical diagnoses entered. It was possible to refer to the hard records to ascertain the clinical diagnoses for all those cases whose computerised record had not been updated. Such a task for the feline and canine databases would have been impossible within the allocated time span. The main advantage of the cattle database was the presence of a post mortem diagnosis for most animals, as further discussed in Chapter 5.

Species	Total cases	Total with biochemistry	Of those, total with Clinical diagnosis	Necropsy
Canine	13172	5818	2361	775
Feline	2379	1052	69	196
Bovine	2072	1225	15	897
Equine	1993	864	667	188

Table 3-4 Summary of number of cases of dogs, cats, cattle and horses seen at GUVS between 1988 and 1995. The numbers of cases which had biochemistry testing carried out as part of their investigation are also given, as well as the number of those which also had a clinical diagnosis or necropsy report entered in the database.

3.7 SUMMARY

The computerised database maintained at GUVS represents a unique and valuable resource. Currently containing records pertaining to a referral population of almost 25,000 animals, the readily searchable database offers a platform for large-scale epidemiological studies. Although, throughout this thesis, investigations will be centred around clinical biochemistry results in equine and bovine animals, the scope for realising information from the raw clinical data is enormous.

Chapter 4 focuses on the application of different statistical techniques to equine clinical biochemistry and diagnosis data extracted from the GUVS hospital database.

CHAPTER IV

INVESTIGATION OF EQUINE BIOCHEMISTRY DATA USING PERCENTILE ANALYSIS AND PROBABILITY TECHNIQUES

CHAPTER IV

INVESTIGATION OF EQUINE BIOCHEMISTRY DATA USING PERCENTILE ANALYSIS AND PROBABILITY TECHNIQUES

"William Harvey was so impressed by the complexity of blood flow that he thought initially the motions of the heart and the blood could be comprehended only by God. Generations of veterinary students since Harvey's time have tended to agree."
Stephenson (1992)

4.1 BACKGROUND

In the fields of both human and veterinary medicine, the realm of ancillary clinical testing has developed enormously in recent years (Fessler, 1984a; Douglas and Eckersall, 1985; Kaneko, 1988; Rao, 1990; Ribble *et al.*, 1990; Christensen, 1992; Young, 1992; Burke, 1995; Sodikoff, 1995). The yearly cost of such testing in human hospitals in the United States has been estimated at over 27 billion dollars (Freudenheim, 1987). In particular, results of clinical biochemistry tests are now readily available to clinicians through the innovation of analysers designed for the practice environment, such as "Vettest 8008" (Little *et al.*, 1992). However, interpretation of these results remains rather subjective, with evaluation based on the experience of the individual clinician, who may refer to means and ranges on the premise that the data are normally distributed, an assumption which may not always be correct. In this chapter, a retrospective study was undertaken to interrogate the clinical biochemistry and diagnosis data maintained within the GUVS hospital database in an attempt to ascertain whether valuable information could be derived from the raw data, with particular emphasis on the possible development of improved means for interpretation. As outlined in 3.6.2, although the equine database was one of the smaller databases, it was one of the most complete with respect to clinical diagnosis data, and was judged to be the most suitable as a basis for initial investigations.

4.2 INTRODUCTION

As both human and veterinary medicines have advanced, so too have the expectations of clients (Colahan *et al.*, 1991; Boon and Easley, 1992). Ancillary clinical testing has reformed the approach to veterinary medicine in the last 15 to 20 years (Tyler and Cullor, 1989; Shimizu *et al.*, 1990). The advent of testing within the consulting room environment has allowed the clinician to perform advanced investigations and helped to provide further guidance towards obtaining a diagnosis, prognosis, and instituting appropriate therapy (Kaneko, 1988; Feldman and Thomason, 1989; Kidd, 1991; Boon and Ealsey, 1992; Mbassa and Poulsen, 1993b; Gerrard and Little, 1994). More specifically, clinical biochemistry offers the practising veterinarian an insight into the health status of the animal patient (Kerr, 1989; Carlson, 1990; Mair *et al.*, 1990; Otesile and Kasali, 1992). It is an invaluable tool in the management of many cases, having a number of potential applications (Magid, 1992; Møller-Peterson, 1992; Fraser and Peterson, 1993). Clinical biochemistry may be used to assist in diagnosis of disease in the unwell animal (Andrews and Reed, 1987; Evans, 1988; Doxey *et al.*, 1991; Eddy, 1992; Mbassa and Poulsen, 1993b); it may be employed to assess severity of disease (Parry, 1987); it may be employed as a means of monitoring the course of a disease process (Feldman and Thomason, 1989) and it may be used as a screening mechanism in animals presumed to be healthy (MacWilliams and Thomas, 1992).

The realisation of the value of clinical biochemistry (Douglas and Eckersall, 1985) has resulted in the advancement of in-house testing techniques (Romatowski, 1994). Plasma biochemistry test results may now be available to the clinician within minutes of examining a patient (Sallee *et al.*, 1990; Little *et al.*, 1992; Hoshi *et al.*, 1994; Tschudi, 1995). Whilst this is advantageous, such test results are only of value when correctly interpreted (Tyler and Cullor, 1989; Dickenson, 1991; Gardner and Holmes, 1993; Schlesinger and Rubin, 1993).

Currently, the standard method for interpretation of clinical biochemistry data is based on what is often termed the "reference range" of a parameter which gives an indication of results which would be expected in a "normal" or healthy animal (Cote and Hoff, 1991; Magid *et al.*, 1992; Okotie-Eboh *et al.*, 1992; Fraser and Peterson, 1993; Mbassa and Poulsen, 1993b; Gascoyne *et al.*, 1994; Kouri *et al.*, 1994). However, most clinicians realise the limitations of the reference range approach, and ultimately it is their experience which enables them to interpret results (Martin, 1988). This experience is

founded on all the cases which they may have encountered previously; effectively, the intellectual database they have developed over a period of years. As with all procedures which rely largely on recall, the reliability of this intellectual database is variable, and the inexperienced clinician is at a disadvantage (Wiener *et al.*, 1990; White, 1993; Burke, 1995; Cockcroft, 1995). The GUVS hospital medical record system offered a large database in which clinico-pathological data had been stored, and provided a means of developing more reliable quantitative measures for clinical biochemistry interpretation.

4.3 MATERIALS

4.3.1 University of Glasgow Hospital Records

Interrogation of the GUVS database identified those horses which had plasma biochemistry testing carried out as part of their referral investigation. The biochemistry results and corresponding clinical diagnoses for each of these cases were used for the study. Although some cases had a number of samples taken for biochemistry investigation, only the first panel of plasma biochemistry results for each case was included in the analysis in order to minimise this source of potential bias. This approach was adopted by Kouri *et al.* (1994) when deriving reference intervals based on hospitalised human patients. A total of 18 plasma biochemistry parameters were selected for investigation: urea, sodium, potassium, chloride, calcium, magnesium, phosphate, creatinine, albumin, globulin, total protein, bilirubin, glucose, creatinine phosphokinase (CPK), alkaline phosphatase (AP), gamma-glutamyl transferase (GGT), cholesterol and aspartate amino-transferase (AST).

4.4 STATISTICAL METHODS

As in the statistical investigation of any data type, the first principles of presenting the raw data in a more meaningful manner applied. This was particularly appropriate for the investigation of the clinical biochemistry data in this study, because the raw data consisted simply of a list of hundreds of data points. Following establishment of the basic distribution of the data, it was possible to apply more informative statistical techniques, as appropriate.

4.4.1 Parameter distribution

A graphical display of the distribution of the results was obtained for each of the biochemistry parameters by creating a histogram showing parameter concentration against frequency. This visual representation of the spread of the parameter results gave an immediate indication of whether or not the data were normally distributed or were skew. For a sample of parameters, a normal distribution curve reflecting the normal range adopted at GUVS was overlaid on the graph achieved from the unwell population. Spreadsheet functions within Microsoft Excel were used to create a table of summary descriptive statistics pertaining to each biochemistry parameter. Of particular interest were the "kurtosis" and "skewness" statistics which further described the distribution of the parameter results.

4.4.2 Percentile analysis

A percentile analysis was performed for each individual biochemistry parameter. Percentile analysis was a simple means of summarising the data whereby parameter results were effectively ranked in order, and then values which separated the data into sections containing one hundredth of the datapoints were identified. Spreadsheet functions within Excel were employed to obtain values for the percentiles of interest, namely, the 1^{st}, 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th} and 99^{th}. The biochemistry results were subsequently grouped into appropriate percentile bands: minimum-1, 2-5, 6-10, 11-25, 26-50, 51-75, 76-90, 91-95, 96-99 and 99-maximum. Expression of all plasma biochemistry results thereafter was in percentile form. Clinical diagnoses corresponding to the biochemistry results were tabulated and ranked according to frequency within each percentile band.

4.4.3 Bayesian approach

In order to ascertain whether knowledge of the concentration of a plasma biochemistry parameter was useful or not, a conditional probability approach was adopted. The probability of a particular diagnosis was calculated both before and after the plasma biochemistry parameter concentration was obtained. To prevent any parameter selection bias affecting the probability results, the prior probability for each diagnosis was based on the cases in which the particular biochemistry parameter had been measured, and therefore had to be calculated separately for each clinical biochemistry parameter. The

prior probability of any diagnosis thus did not necessarily reflect the true prevalence of a diagnosis within the hospital population, rather it reflected the prevalence of the disease for each biochemistry parameter. The prior probability of a particular diagnosis, *a priori*, was calculated using Equation 4-1 and was termed Pr(D).

$$\Pr(D) = \frac{\text{Number of cases with diagnosis D}}{\text{Total number of cases}}$$

Equation 4-1 Equation used to calculate the prior probability of diagnosis D. This equation was applied to the most common diagnoses for each clinical biochemistry parameter investigated.

The posterior probability, *a posteriori*, was calculated as the probability of a particular diagnosis, given that the biochemistry parameter concentration was located within a particular percentile band, as shown in Equation 4-2. This was regarded as the probability of a particular diagnosis given the new biochemistry information and was termed Pr(D|B), which may be read "probability of D *given* B".

$$\Pr(D|B) = \frac{\text{Number of cases with diagnosis D, given percentile band B}}{\text{Total number of cases in percentile band B}}$$

Equation 4-2 Equation used to calculate the posterior probability of diagnosis D, given that the biochemistry parameter concentration was located within a particular percentile band B.

Using this information and applying Bayesian philosophy, first proffered in 1763 (Pearson and Kendall, 1970), the value of knowing the biochemistry value for a parameter for a particular disease was assessed.

By using the concept of "odds", the ratio of 'the probability that something is so' to 'the probability that something is not so' (Møller-Peterson, 1992), in a manner similar to the calculation of the prior and posterior probabilities for diagnoses, prior and posterior odds were calculated. The prior odds thus represented the odds in favour of a particular diagnosis before any biochemistry measurement was known, and was calculated using the Equation 4-3.

$$\text{prior odds} = \frac{\text{Probability of diagnosis D}}{\text{Probability of not diagnosis D}}$$

Equation 4-3 Equation used to calculate the prior odds of diagnosis D. This equation was applied to each of the most common diagnoses for each clinical biochemistry parameter investigated.

The posterior odds represented the odds in favour of a particular disease given the biochemistry information (Equation 4-4).

$$\text{posterior odds} = \frac{\text{Prob. of diag. D, given parameter value within percentile band B}}{\text{Prob. of not diag. D, given parameter value within percentile band B}}$$

Equation 4-4 Equation used to calculate the posterior odds of diagnosis D. This equation was applied to each of the most common diagnoses within each percentile band grouping for each clinical biochemistry parameter investigated.

However, the information which was of particular interest was that which represented the effect which the new biochemistry information had on the odds in favour of each diagnosis. Using rules of conditional and multiplicative probability, a ratio was derived. In general terms, the multiplicative axiom of probability states: The probability that two events, A and B, will both occur is equal to the probability of B multiplied by the probability of A given that B has already occurred (Equation 4-5).

$$P(A \cap B) = P(B).P(A|B)$$

Equation 4-5 The multiplicative axiom of probability which states that the probability that two events, A and B, will both occur is equal to the probability of B multiplied by the probability of A given that B has already occurred.

From this equation, the formula for conditional probability follows (Equation 4-6).

$$P(B|A) = \frac{P(A \cap B)}{P(A)}$$

$$P(B|A) = \frac{P(B) \,.\, P(A|B)}{P(A)}$$

Equation 4-6 The axiom for conditional probability which states that the probability of event B occurring, given that event A has already occurred, is the probability of B multiplied by the probability of A given B, divided by the probability of A.

Now, the probability of event B not occurring may be similarly expressed (Equation 4-7).

$$P(B'|A) = \frac{P(B') \,.\, P(A|B')}{P(A)}$$

Equation 4-7 The axiom for conditional probability which states that the probability of event B not occurring, given that event A has already occurred, is the probability of B not occurring multiplied by the probability of A given B has not occurred, divided by the probability of A.

As described, the ratio of Equation 4-6 to that of Equation 4-7 gives the odds in favour of B given A and may be expressed as shown in Equation 4-8.

$$\frac{P(B|A)}{P(B'|A)} = \frac{P(A|B).P(B)}{P(A|B').P(B')}$$

Equation 4-8 The odds in favour of event B occurring given that event A has already occurred.

By applying these methods to the particular situation regarding diagnosis and biochemistry results, the Bayesian Equation 4-9 was derived.

$$\frac{Pr(D|B)}{Pr(D'|B)} = \frac{Pr(B|D).Pr(D)}{Pr(B|D').Pr(D')}$$

Where, D represents diagnosis, D' represents all diagnoses which are not diagnosis D, and B represents percentile band B.

Equation 4-9 Equation which represents the odds in favour of diagnosis D given a biochemistry parameter value in percentile band B.

The interpretation of Equation 4-9 may be simplified by examining the three important ratios into which it may be divided. The ratio Pr(D|B)/Pr(D'|B) may be regarded as the odds in favour of the diagnosis after the parameter concentration is known, that is, the odds in favour of the diagnosis, given that the parameter concentration lies in percentile band B. The ratio Pr(D)/Pr(D') may be regarded as the odds in favour of the diagnosis before the parameter concentration is known, that is, the odds in favour of the diagnosis before any biochemistry information is known.

The middle ratio, P(B|D)/P(B|D'), was of particular importance. This likelihood ratio was termed the "Biochemical Factor". The Biochemical Factor represented the gain in information derived from using the database to quantify the relationship between the

biochemistry percentile bands and the probability of different diseases. The Biochemical Factor was calculated for each diagnosis, within each percentile band, for each biochemistry parameter.

4.5 RESULTS

4.5.1 Summary Statistics

A total of 740 equine referral cases were identified as suitable for inclusion in the study because biochemistry testing had been undertaken as part of their investigation. Table 4-1 shows the frequency with which plasma biochemistry samples were taken. The majority (51%) of cases had only one biochemistry sample taken, on which a number of different biochemistry parameters were measured. However, the number of biochemistry samples taken from an individual animal ranged from 1 to 34. The mean number of biochemistry samples taken per horse was 2.7. The analysis was carried out on the first panel of results only, preventing any potential bias which may have arisen from including subsequent panels from the same horse.

No. of samples taken per horse	Frequency
1	371
2	133
3	84
4	46
5	26
6	19
7	18
8	9
9	3
10	7
10+	24

Table 4-1 Frequency with which plasma biochemistry samples were taken from a total of 740 equine referral cases seen at GUVS hospital.

Table 4-2 shows the number of times each biochemistry parameter was measured within the first biochemistry panel. There was some variation in the frequency with which biochemistry parameters had been selected within panels, but a core of 14 parameters had been measured in most cases, namely, urea, alkaline phosphatase, creatinine, total protein, albumin, globulin, aspartate amino-transferase, sodium, potassium, chloride,

bilirubin, calcium, phosphate and magnesium. Further analysis focused on the core of 14 parameters.

Biochemistry parameter	Total cases
Urea	677
Alkaline phosphatase	677
Creatinine	661
Total protein	656
Albumin	654
Globulin	652
Aspartate amino-transferase	647
Sodium	637
Potassium	636
Chloride	631
Bilirubin	627
Calcium	607
Phosphate	599
Magnesium	577
Cholesterol	396
Gamma-glutamyl transferase	282
Creatinine phosphokinase	247
Glucose	107

Table 4-2 Frequency with which each biochemistry parameter was measured within the first biochemistry panel of 740 equine cases from GUVS hospital.

4.5.2 Biochemistry parameter distributions

Histograms which displayed the distribution of results were constructed for each biochemistry parameter and suggested that most of the parameters did not follow a normal distribution. For example, Figure 4-1 demonstrates that the distribution of albumin was skew with a tail to the left and Figure 4-2 shows the distribution of urea with a tail to the right. Figures 4-3 and 4-4, for plasma albumin and plasma urea results, respectively, similarly show the distribution of results from the putatively unwell GUVS referral population, together with the theoretical normal distribution based on the GUVS reference range for comparison.

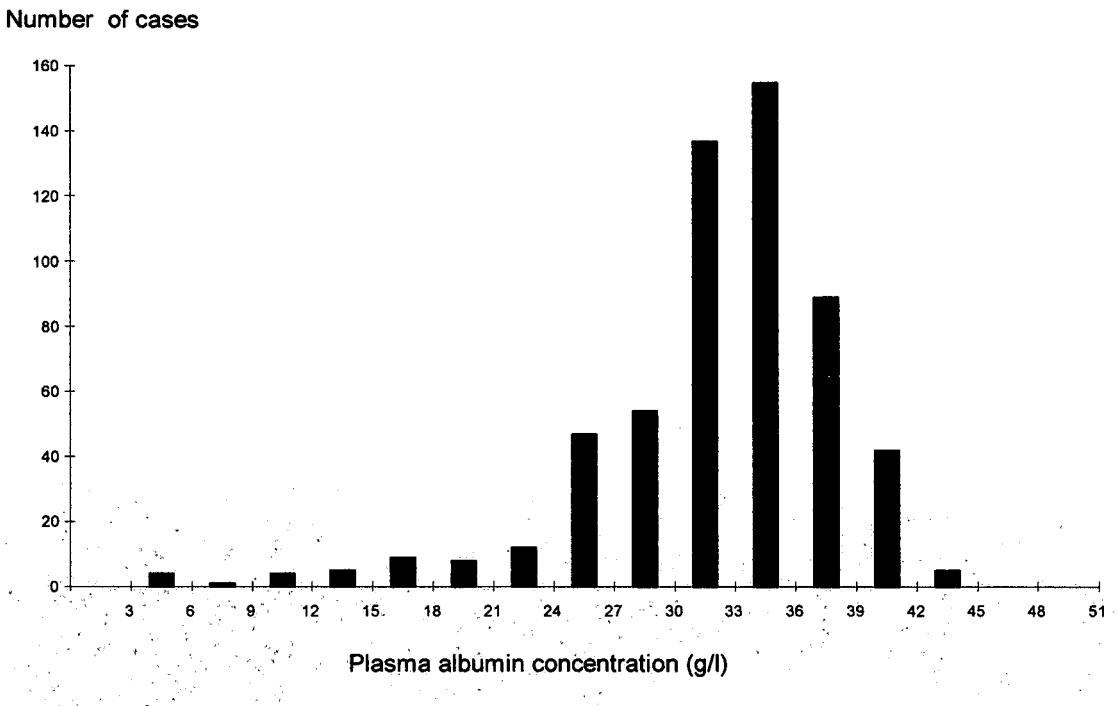


Figure 4-1 Distribution of plasma albumin results (g/l) from equine referral cases seen at GUVS over the period of the study.

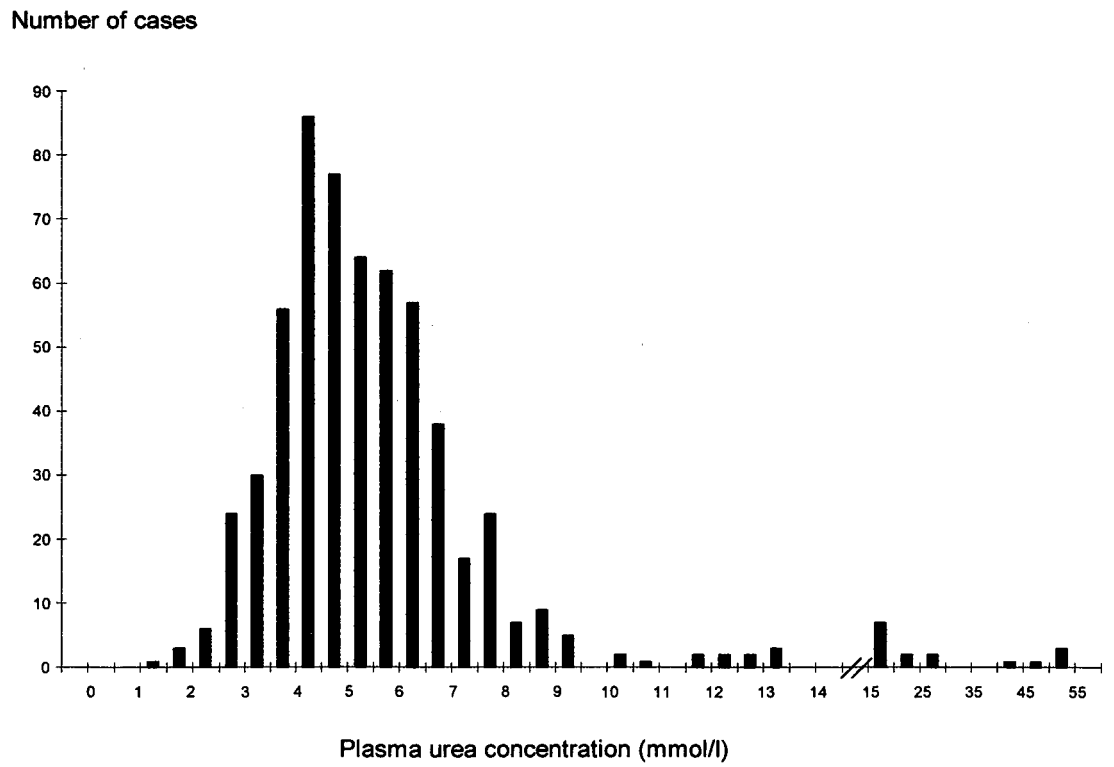


Figure 4-2 Distribution of plasma urea results (mmol/l) from equine referral cases seen at GUVS over the period of the study.

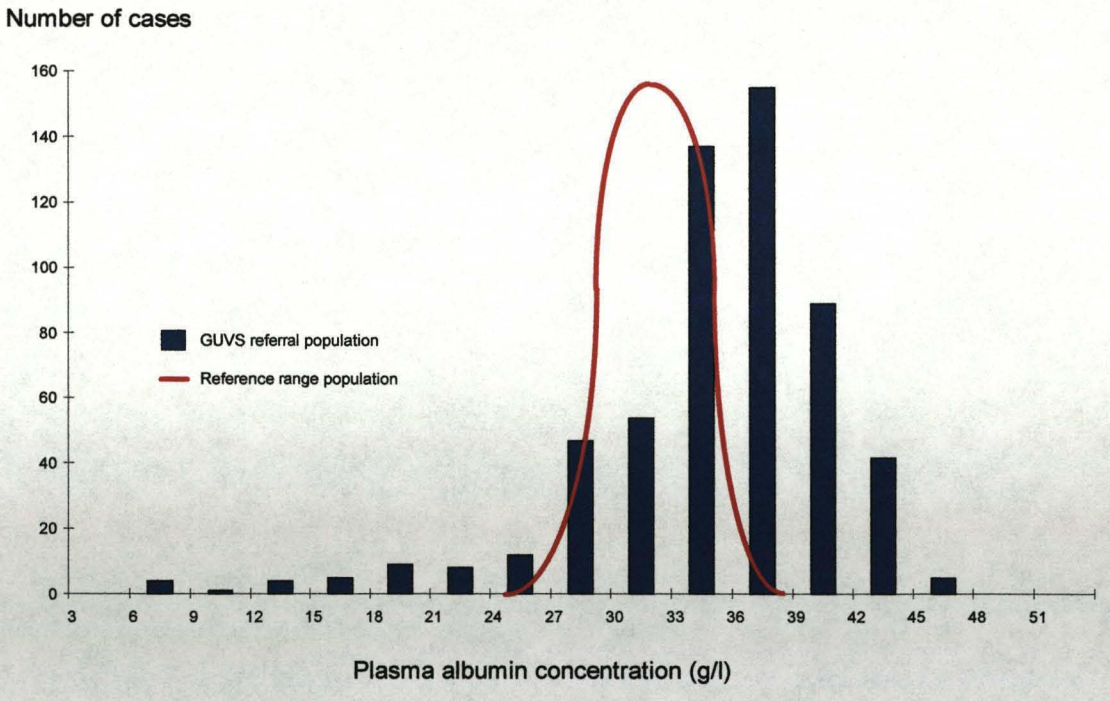


Figure 4-3 Distribution of plasma albumin results (g/l) from equine referral cases seen at GUVS over the period of the study, overlaid with the theoretical distribution based on the GUVS reference range.

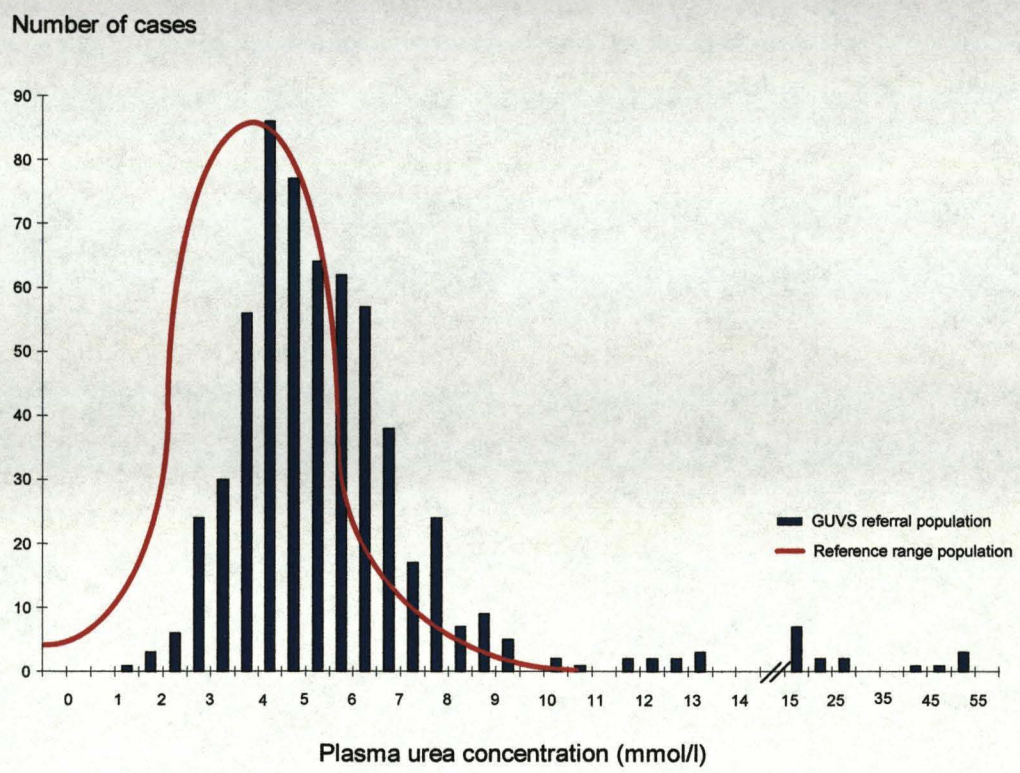


Figure 4-4 Distribution of plasma urea results (mmol/l) from equine referral cases seen at GUVS over the period of the study, overlaid with the theoretical distribution based on the GUVS reference range.

Table 4-3 shows the descriptive statistic summaries for plasma albumin and urea. Positive kurtosis indicated a relatively peaked distribution whereas negative kurtosis indicated a relatively flat distribution. Skewness characterised the degree of asymmetry of a distribution around its mean. Positive skewness indicated a distribution with an asymmetric tail extending towards more positive values, that is, towards the right. Negative skewness indicated a distribution with an asymmetric tail extending towards more negative values, that is, towards the left.

	Biochemistry parameter	
Statistic	Albumin (g/l)	Urea (mmol/l)
Mean	32.6	6.045
Standard Error	0.3	0.220
Median	34	5.12
Mode	33	4.20
Standard Deviation	6.1	5.361
Kurtosis	3.91	56.00
Skewness	-1.59	6.89
Range	38	59.63
Minimum	5	1.50
Maximum	43	61.13

Table 4-3 Descriptive statistics for plasma albumin results and plasma urea results from equine referral cases seen at GUVS over study period.

In keeping with the graphical presentations of the data, the skewness for the plasma albumin was negative, while that for the plasma urea results was positive. None of the biochemistry parameters conformed to a normal distribution, although the kurtosis and skewness varied depending on the parameter. The majority of parameters had positive skewness, indicative of a tail to the right. However, sodium, chloride, calcium, albumin and total protein had negative skewness. The descriptive statistics for each of the biochemistry parameters are listed in Appendix I.

4.5.3 Percentile analysis

Table 4-4 shows the results which were achieved when a percentile analysis was performed for each plasma biochemistry parameter. The minimum value, the 1st, 5th, 10th, 25th (i.e. lower quartile), 50th (i.e. median), 75th (i.e. upper quartile), 90th, 95th and 99th percentiles, and the maximum value are shown for each parameter. The table may be

interpreted for each parameter as follows. The results tabulated for urea show that the 50th percentile (i.e. median) was 5.120 mmol/l. Continuing to use urea as an example, Table 4-4 shows that 25% of the values achieved were below 4.155 mmol/l, and similarly that only 1% of the values were below 2.374 mmol/l. Thus, the table indicates how the results achieved for each of the plasma biochemistry parameters from the putatively unwell hospital population were spread. Table 4-5, which displays the reference range adopted at GUVS for each parameter, has been included to allow a comparison between the reference range and the percentile approach.

Parameter	Units	Reference range
Urea	mmol/l	0 - 8.84
AP	U/l	18 - 280
Creatinine	µmol/l	62 - 133
Total protein	g/l	50 - 83
Albumin	g/l	26-35
AST	U/l	90 - 240
Globulin	g/l	30-35
Sodium	mmol/l	130 - 151
Potassium	mmol/l	2.6 - 5.2
Chloride	mmol/l	94 - 113
Bilirubin	µmol/l	0 - 25.8
Calcium	mmol/l	2.78 - 3.38
Phosphate	mmol/l	0.9 - 1.93
Magnesium	mmol/l	0.69 - 1.27

Table 4-5 GUVS equine reference ranges for plasma biochemistry parameters.

Parameter	Units	Min.	Percentile 1%	5%	10%	25%	50%	75%	90%	95%	99%	Max.
Urea	mmol/l	1.500	2.374	2.904	3.404	4.155	5.120	6.280	7.700	9.417	30.259	61.130
AP	U/l	1.0	53.5	158.6	187.0	245.8	343.5	501.3	776.7	1120.8	2717.5	6700.0
Creatinine	µmol/l	14.0	59.4	82.9	92.0	106.0	123.0	143.0	162.0	183.2	664.1	4050.0
Total protein	g/l	15.0	32.0	52.0	58.0	63.0	67.0	73.0	78.0	81.0	90.4	130.0
Albumin	g/l	5.0	10.0	21.0	26.0	30.0	34.0	36.0	39.0	40.0	42.0	43.0
AST	U/l	11.0	30.4	182.6	210.0	245.0	292.0	375.2	538.5	711.7	1415.9	3740.0
Globulin	g/l	10.0	16.6	23.0	26.0	29.0	33.0	40.0	45.0	49.9	64.9	117.0
Sodium	mmol/l	104	119	130	131	135	137	139	140	142	148	159
Potassium	mmol/l	1.30	2.10	2.50	2.80	3.20	3.60	4.00	4.40	4.91	6.60	10.50
Chloride	mmol/l	49.0	77.2	88.8	92.0	96.0	98.0	101.0	103.0	105.0	113.4	124.0
Bilirubin	µmol/l	1.0	2.0	9.0	12.0	17.2	26.0	39.0	61.1	78.1	108.5	169.0
Calcium	mmol/l	0.590	1.929	2.404	2.610	2.810	2.950	3.090	3.190	3.236	3.407	3.570
Phosphate	mmol/l	0.270	0.420	0.570	0.630	0.790	1.000	1.300	1.706	2.060	2.796	4.750
Magnesium	mmol/l	0.250	0.370	0.460	0.520	0.590	0.660	0.720	0.770	0.817	1.137	3.170

Table 4-4 Results of percentile analysis performed on each of the biochemistry parameters investigated. Results are based on a maximum of 740 equine referral cases seen at GUVS over the period of the study.

4.5.4 Differential diagnoses

Table 4-6 shows the frequency of the ten most common diagnoses from those cases which had urea measured, medical colic being the most common diagnosis. Of all the cases investigated, only 203 fell within the ten most common diagnoses. This was a reflection of the nature of cases which present to a referral hospital. The frequency tables varied slightly among biochemistry parameters. This may have reflected the biochemistry parameter selection bias which arose due to the clinician's prior knowledge of the clinical presentation of a case.

Diagnosis	Frequency
Medical colic	33
Sarcoids	25
Chronic obstructive pulmonary disease	22
Cryptorchid	22
Surgical colic	20
Laminitis	19
Cushing's disease	18
Hepatopathy	17
Laryngeal hemiplegia	14
Grass sickness	13

Table 4-6 The frequency of the ten most common diagnoses, for those equine cases which had plasma urea measured as part of their investigation.

4.5.5 Biochemical Factor

Table 4-7 shows the Biochemical Factor results which were calculated for plasma urea using the information within the database. As an example, let us suppose that the database contained urea values for 500 horses. Of these 500 horses, 50 were diagnosed as having hepatopathy and the remaining 450 did not have hepatopathy. Of the 50 which were diagnosed as having hepatopathy, suppose 15 had a urea value which lay in the "26^{th} to 50^{th} percentile band", i.e. greater than 4.155 mmol/l and less than or equal to 5.120 mmol/l. By the nature of percentile analysis, if the database contained 500 horses, then 125 of the results would lie in the "26^{th} to 50^{th} percentile band". The Biochemical Factor for hepatopathy within the "26^{th} to 50^{th} percentile band" would be calculated as follows:

$$\frac{Pr(B|D)}{Pr(B|D')} = \frac{15/50}{110/450} = 1.2$$

This indicates that the prior odds in favour of hepatopathy would not be significantly increased with such a urea result. Similarly, suppose ten of the horses which had been diagnosed as having hepatopathy had a urea value which lay in the "2nd to 5th percentile band", i.e. was greater than 2.374 mmol/l and less than or equal to 2.904 mmol/l. The Biochemical Factor for hepatopathy within the "2nd to 5th percentile band" would be calculated as follows:

$$\frac{Pr(B|D)}{Pr(B|D')} = \frac{10/50}{10/450} = 9.0$$

This indicates that such a low urea value would increase the odds in favour of hepatopathy nine-fold.

Using the information from the equine cases from within the hospital database, the Biochemical Factor was similarly calculated for each diagnosis within each percentile band for urea (Table 4-7). The higher Biochemical Factors lay in the uppermost and lowermost percentile bands. Within the middle 50 percent of cases, that is, between the 25th and 75th percentile values, the Biochemical Factor was approximately 1 or 2 for the majority of the diagnoses. This reflected the fact that most of the information value when interpreting the urea test results lay in those cases which had markedly raised or lowered values. From Table 4-7 it can be seen that the Biochemical Factor for a given diagnosis varied depending on the value of urea obtained. For example, when the urea value lay within the 2nd to 5th percentile band, hepatopathy was three times more likely, but when the urea value lay in the lowest 1 per cent of cases, it was almost 16 times more likely. This highlighted the increased information value which may be obtained if interpretation of clinical biochemistry results is undertaken using a combination of the percentile and probabilistic approaches, rather than using a "reference range".

Not only does Table 4-7 emphasise the value of knowing a urea result with respect to how likely a particular diagnosis is, it also reflects the changing pattern of diagnoses given different urea results. This is supported by the fact that the list of the most common diagnoses was different within each percentile band. For example, from Table 4-6, it can be seen that medical colic was the most common diagnosis, irrespective of the urea value. However, from Table 4-7, it can be seen that if the urea value lay within the "minimum to 1st" percentile band then the most common diagnosis was hepatopathy; whereas if the urea value lay in the "99th to maximum percentile band", then the most common diagnosis was nephropathy.

Percentile Band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Hepatopathy	15.6
2 - 5	Medical colic	2.3
	Tooth root abscess	6.0
	Colitis	5.5
	Hepatopathy	3.0
	Laminitis	2.5
6 - 10	Chronic enteropathy	9.0
	Medical colic	1.2
	COPD*	1.8
11 - 25	Sarcoids	1.4
	Cushing's disease	1.5
	Laminitis	1.4
	Medical colic	0.6
	COPD	1.0
	Laryngeal hemiplegia	1.4
26 - 50	Laminitis	1.3
	Navicular disease	1.6
	Sarcoids	0.8
	Surgical colic	0.8
	Tooth root abscess	1.3
51 - 75	Cushing's disease	2.2
	Sarcoids	1.6
	Medical colic	1.0
	Surgical colic	1.5
	COPD	1.4
76 - 90	Medical colic	1.8
	Cryptorchid	3.0
	Surgical colic	1.4
	COPD	1.3
	Hepatopathy	1.8
	Grass sickness	1.6
	Squamous cell carcinoma	2.7
91 - 95	Medical colic	1.9
	Grass sickness	4.8
	Sarcoids	2.5
	Laryngeal hemiplegia	2.8
96 - 98	Medical colic	2.4
	Grass sickness	6.2
	Hyperlipaemia	11.6
	Surgical colic	2.6
	Colitis	5.7
99 - max.	Nephropathy	34.0

*Chronic obstructive pulmonary disease

Table 4-7 Biochemical Factor calculated for the most common diagnoses, within each percentile band for plasma urea from GUVS equine referral cases.

Percentile Band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Medical colic	6.3
2 - 5	Medical colic	2.3
	Colitis	8.3
	Chronic enteropathy	9.6
	Hepatopathy	4.8
	Alimentary lymphosarcoma	15.1
	Larval cyathostomiasis	15.1
6 - 10	Hepatopathy	4.6
	Surgical colic	3.2
	Colitis	3.8
	Chronic enteropathy	11.7
11 - 25	Medical colic	1.2
	COPD*	1.7
	Hepatopathy	1.9
	Squamous cell carcinoma	3.7
	Laminitis	1.3
	Sarcoids	1.0
26 - 50	Navicular disease	1.7
	Medical colic	0.7
	Surgical colic	1.3
	COPD	0.9
	Tooth root abscess	1.7
51 - 75	Cryptorchid	2.0
	Cushing's disease	1.5
	Laryngeal hemiplegia	2.2
	COPD	0.9
	Grass sickness	1.4
	Laminitis	1.1
76 - 90	Medical colic	2.2
	Sarcoids	2.0
	Laminitis	2.1
	COPD	1.3
	Cushing's disease	1.3
91 - 95	Medical colic	1.6
	Cushing's disease	3.1
96 - 99	Laminitis	7.6
	Grass sickness	5.4
99 - max.	Grass sickness	13.6

*Chronic obstructive pulmonary disease

Table 4-8 Biochemical Factor calculated for the most common diagnoses, within each percentile band for plasma albumin from GUVS equine referral cases.

Table 4-8 shows the Biochemical Factor results for plasma albumin. Similarly, most of the information value lay in the outermost percentile bands. Noticeably, the lowermost five to ten percent of cases provided clinically sensible differential diagnoses for low plasma albumin. The percentile based differential diagnosis lists and associated Biochemical Factors for each of the other biochemistry parameters are included in Appendix II.

4.6 DISCUSSION

Although clinical biochemistry may be used as a health screening mechanism, for example to assess severity of dehydration, the emphasis of this study was on the investigation of clinical biochemistry as a diagnostic tool. A number of key issues in this respect were: adoption of a percentile approach for the interpretation of clinical biochemistry; application of probability techniques to parameter selection and diagnostic support; and the requirement for improved clinical biochemistry interpretation guidelines.

However, one of the main considerations raised within this study must be briefly highlighted. The diagnoses used in this study were clinical diagnoses. Given that a diagnosis may have been made with the aid of clinical biochemistry results, then the clinical biochemistry results may show an association with that diagnosis. A circular argument thus ensues. Although an important recognition, this circular argument is unlikely to have influenced the results to a large extent since most clinical diagnoses are made using all the information available to the clinician: historical, clinical, haematological, biochemical, pathological, and so on, rather than relying on any one parameter result (Martin and Bonnett, 1987; Gräsbeck, 1990; Cote and Hoff, 1991; Young, 1992). However, as it may be argued that some of the results in this study were indeed derived from expert opinion, overcoming this problem would require a definitive diagnosis to be available for every case. Such diagnoses were not available for the equine population, but maintained at GUVS was a database containing *post mortem* diagnoses for a large number of cattle cases. Interrogation of the cattle population was therefore similarly undertaken using the statistical techniques described. Each of the issues pertaining to the implications of the findings from interrogation of the equine database are therefore further discussed in Chapter 5, following analysis of the cattle population.

CHAPTER V

BOVINE BIOCHEMISTRY DATA ANALYSIS - PART I
PERCENTILE ANALYSIS AND PROBABILITY TECHNIQUES

CHAPTER V

BOVINE BIOCHEMISTRY DATA ANALYSIS - PART I
PERCENTILE ANALYSIS AND PROBABILITY TECHNIQUES

"Medicine is a science of uncertainty and an art of probability"

Sir William Osler (1849 - 1919)

5.1 INTRODUCTION

The equine clinical biochemistry and diagnosis data from the GUVS hospital database were investigated using percentile analysis and probability techniques as described in Chapter 4. One of the issues associated with the development of the objective means of clinical biochemistry interpretation developed using the equine database was that the diagnoses used were clinical diagnoses. As such, these diagnoses may have been influenced by the clinical biochemistry profile. As explained in section 4.6, this is unlikely to have affected the Biochemical Factor results significantly. However, the bovine database maintained at GUVS offered *post mortem* diagnoses for all cases investigated, and therefore provided a means by which the Biochemical Factor results could be independently assessed (Smith, 1991a).

This chapter outlines the percentile analysis and Bayesian probability methods as applied to the cattle population from GUVS. Some of the procedures and concepts mirror those applicable to the equine population as described in Chapter 4. In order that this chapter (Chapter 5) remains complete and fully comprehensible, a degree of re-iteration of key facts and procedures is necessary. However, to reflect the increasing familiarity with both the GUVS database query language and with Microsoft Excel spreadsheet functions that the investigation of an additional species allowed, this chapter also focuses on data manipulation techniques employed.

5.2 MATERIALS AND METHODS

5.2.1 Source of data

Through the approach to undergraduate teaching of large animal clinical studies at GUVS, a large cattle database has been maintained for a number of years. During the period covered by the study, those cattle cases considered as economic losses to the farmer were purchased for teaching purposes. Each received a thorough clinical investigation and detailed work-up, and was ultimately euthanased. Every case included in the study received a *post mortem* examination. Using the query language to interrogate the hospital database, relevant data pertaining to cattle cases which presented to GUVS over the study period spanning approximately nine years were extracted. For each case, a panel of plasma biochemistry test results and the corresponding *post mortem* diagnosis were retrieved. The panel of biochemistry results under consideration was the last panel available, because it was nearest the time of the *post mortem*. The eighteen plasma biochemistry parameters which were investigated were urea, sodium, potassium, chloride, calcium, magnesium, phosphate, creatinine, albumin, globulin, total protein, bilirubin, glucose, creatinine phosphokinase (CPK), alkaline phosphatase (AP), gamma-glutamyl transferase (GGT), cholesterol and aspartate amino-transferase (AST). The data were imported to a Microsoft Excel workbook for subsequent analysis.

5.2.2 GUVS database queries

As detailed in 3.4.5, it was not possible to output both the biochemistry results and the *post mortem* diagnoses for a selection of cases from the GUVS hospital database simultaneously. Instead, the biochemistry file and the necropsy file were interrogated separately, and the data combined at a later stage within Excel. This demanded that two separate queries be performed: one to extract the biochemistry data and a second to extract the *post mortem* diagnosis data.

5.2.2.1 Extraction of clinical biochemistry data

The GUVS database file which contained the necessary data was the "Biochemistry file". The animals of interest were cattle which had biochemistry testing carried out as part of their investigation, and which also had a *post mortem* diagnosis recorded.

The selections which fulfilled this requirement were as follows:

Species	=	3
Last_bioc	>	0
Last_necro	>	0

The parameters which were output for each case included the hospital number for identification; the date the sample was collected and the date the laboratory received the sample; the biochemistry panel number (e.g. 1st panel, 2nd panel, etc.); the results for the 18 biochemistry parameters of interest; the type of sample (e.g. plasma/ urine/ etc.); and various case description details (such as breed). The fields selected for output from the biochemistry file were therefore as follows:

Hosp_no	Phos	CPK
Date_Coll	Sugar	GGT
Date_Recv	Chol	Sam_type
Ref2	Creat	Breed1
Urea	Bil	Breed2
Sodium	S_alk_phos	DOB
Potas	AST	Sex
Chlor	Tot_prot	Date_first_seen
Cal	Alb	Date_last_seen
Magnes	Glob	

The output file was saved as a "comma delimited" file, for ease of eventual export to Excel.

Although it was simple to extract the electronic biochemistry data as described, there was a problem with a proportion of the data derived from the hospital database. Over the time period spanned by the study for the investigation of cattle biochemistry, the analyser used for generation of the biochemistry results had been changed. This was not only of importance for the statistical analysis which was to be undertaken, but was also of importance with respect to the reliability of the data. Until the more recent AXON Biochemistry Analyser (Appendix VII) was installed on 1st March 1995, all biochemistry results generated at GUVS had been automatically uploaded to the computerised hospital database. However, the AXON Biochemistry Analyser was not compatible with the software systems in place, and the data generated could not be automatically uploaded, rather they were input manually by technical staff. Due to the fact that transcription errors were probable, it was necessary to compare all the electronic biochemistry results generated using the AXON Biochemistry Analyser with

those from the rigorously maintained clinical biochemistry laboratory day-books. Identification of outliers only was not sufficient for the purposes of the statistical analysis which was subsequently undertaken.

5.2.2.2 Extraction of post mortem *diagnosis data*

The GUVS database "Necropsy file" was that which contained all the necessary *post mortem* diagnosis data. The animals of interest were the same as those required for *5.3.2.1*, therefore the selection for cases was the same as above.

The parameters to be output for each case included hospital number; the date on which the carcass was sent to the laboratory, the date on which it was received by the laboratory, and the date the final *post mortem* report was written; the reference pertaining to the pathologist in charge of the case; the first five *post mortem* diagnoses established (e.g. ventricular septal defect), with associated details of site (e.g. heart) and classification (e.g. congenital); the pathologist's comments; and various case description details. The necropsy file output, which was saved as "comma delimited", contained the following parameters:

Hosp_no	Site2	Site5
Date_sent	Class2	Class5
Date_recv	Diag3	Commenttext
Date_report	Site3	Breed1
Pathologist	Class3	Breed2
Diag1	Diag4	DOB
Site1	Site4	Sex
Class1	Class4	Date_first_seen
Diag2	Diag5	Date_last_seen

Although the first five *post mortem* diagnoses were output, only the primary diagnosis, "Diag1" and associated site were used for statistical analysis.

5.3 STATISTICAL METHODS

The statistical methods employed to summarise and analyse the bovine clinical biochemistry and diagnosis data were mainly as detailed for the equine data in Chapter 4. The methods will be briefly described.

5.3.1 Parameter distribution

For each biochemistry parameter, a histogram displaying plasma concentration against frequency was created in Excel. Excel spreadsheet functions were also employed to calculate descriptive statistics for each of the biochemistry parameters. Both of these statistical methods gave an indication as to whether the biochemistry parameters were normally distributed or not.

5.3.2 Percentile analysis

During the nine year period spanned by the project, a total of three biochemistry analysers (Appendix VII) had been used to generate the biochemistry results for the GUVS cattle cases. It is recognised that when different techniques are used to achieve biochemistry data, the results can vary slightly (Pickrell *et al.*, 1974; Farver, 1989; Carlson, 1990; Young, 1992; Fraser and Peterson, 1993). It was therefore necessary to separate the biochemistry data which had been extracted from the GUVS database into three appropriate groups, reflecting data generated from each of the three analysers. Subsequently, for the 14 biochemistry parameters under investigation, percentile analyses treating the data from the three analysers separately were performed. Furthermore, two percentile analyses were undertaken for each parameter because interest lay in both irregular and regular percentile band groupings.

Those irregular percentiles which were calculated were as in Chapter 4, that is, the 1^{st}, 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th} and 99^{th}. The regular percentiles which were calculated were the 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th}, 60^{th}, 70^{th}, 80^{th}, and 90^{th}. The biochemistry results were subsequently grouped into appropriate percentile bands based on the percentile analyses. In effect, there were two basic sets of analysis being undertaken in tandem: analysis based on irregular percentile groupings and analysis based on regular percentile groupings.

Absolute values from this stage hence in the study were unnecessary and expression of all plasma biochemistry results was in percentile form. Consequently, the data derived from each of the three analysers were combined in coded percentile form for further analysis. The diagnosis data were also later coded to facilitate data manipulation (5.4).

5.3.3 Random selection of training dataset

In Chapter 6, a pattern recognition technique is discussed which details biochemistry profiles for a selection of the more common diseases noted within the GUVS cattle database. In order for the pattern recognition technique to be assessed, a "training set" and a "test set" of data were required. Briefly, a training set is used to achieve a set of expected results, and the test set is used as a means of independently assessing those results. The probability methods discussed in this chapter (5.3.4) could have been carried out on the entire dataset, but, given that the training and test sets were required for further pattern recognition analysis in Chapter 6, this chapter details the results achieved using the training set only. It was thus necessary at this stage to divide the data into two sets. The training set was created after the percentile analysis and biochemistry coding were completed.

The training set required consisted of approximately two-thirds of the entire dataset. One method which could have been used to derive the training set was to select data from, for example, all cases seen between 1988 and 1995. The test set would then have consisted of all cases seen between 1995 and July 1997. However, this method of developing the test set was unsatisfactory due to the time component within the two datasets. In order to avoid temporal bias, it was more appropriate to extract all the cases over the study period, 1988 to 1997, and randomly select two-thirds of the cases to act as the training set. The statistical package Minitab (Minitab Inc.) was used to achieve the random sample of cases required.

5.3.4 Probability techniques

The probability methods as detailed in 4.4.3 were undertaken on both the irregular and regular percentile band groupings for each clinical biochemistry parameter. Only those biochemistry parameters which had been frequently selected for measurement were used for calculation of the Biochemical Factor. These fourteen parameters were urea, sodium, potassium, chloride, calcium, magnesium, phosphate, creatinine, bilirubin, alkaline phosphatase, aspartate amino-transferase, total protein, albumin and globulin.

5.4 DATA MANIPULATION METHODS

In order to facilitate data handling and statistical analysis using spreadsheet functions, the data were coded where possible. In particular, the clinical biochemistry and *post mortem* diagnosis data were represented in coded format.

5.4.1 Coding of biochemistry data

As outlined in 5.3.2, after percentile analysis was performed, all data were represented in percentile form, rather than with an absolute concentration value. There were two basic approaches to the probabilistic analysis being carried out in tandem on identical copies of the original clinical biochemistry and diagnosis data: one based on irregular percentile band groupings, the other based on regular percentile band groupings. Table 5-1 outlines the coding used for the clinical biochemistry data, subsequent to percentile analysis, for both of the approaches.

Percentile Band		Code
Irregular approach	Regular approach	
Min. - 1	Min. - 10	1
2 - 5	11 - 20	2
6 - 10	21 - 30	3
11 - 25	31 - 40	4
26 - 50	41 - 50	5
51 - 75	51 - 60	6
76 - 90	61 - 70	7
91 - 95	71 - 80	8
96 - 99	81 - 90	9
99 - Max.	91 - Max.	10

Table 5-1 Representation of coding adopted for clinical biochemistry data based on percentile band groupings, for both the regular and irregular approach.

5.4.2 Coding of *post mortem* diagnoses

The coding of the *post mortem* diagnoses was undertaken in two ways. First, the majority of the diagnoses taken directly from the query of necropsy file database were manually coded using a simple numerical system. For those diagnoses which appeared only once, no coding was indicated. Table 5-2 details the diagnosis coding system.

The second approach to the coding of the *post mortem* diagnoses was based on the site classification determined by the pathologist at the time of *post mortem* examination. This "site" parameter was extracted from the database when the necropsy

database was interrogated (e.g. Site_1) (Section *5.2.2.2*). Table 5-3 outlines the details of the site classification system which was developed by pathologists at GUVS.

Post mortem diagnosis	Code	*Post mortem* diagnosis	Code
Abscessation	2	Leukodystrophy	38
Actinobacillosis	3	Hepatic lipidosis	39
Arthritis	4	Lymphosarcoma	40
Arthrogryphosis	5	MCF[‡‡]	41
Bladder-rupture	6	Meningoencephalitis	42
Bloat	7	Metritis	43
BPS[*]	8	Mucosal disease	44
Bronchitis	9	Myocardial problem	45
Carcinoma	10	Myopathy-nutritional	46
Cardiomyopathy	11	Nephritis	47
Cataracts	12	Nephrosclerosis-juvenile	48
CCN[†]	13	Neuropathy-peripheral	49
Cellulitis	14	Omphalophlebitis	50
Cerebellar hypoplasia	15	Osteomyelitis	51
Fascioliasis	16	Ostertagiasis	52
Cirrhosis	17	Pericarditis	53
Cleft palate	18	Pericarditis traumatic	54
Congenital cardiac defect	19	Peritonitis	55
Congenital cataracts	20	Pleuritis	56
Cor pulmonale	21	Pneumonia	57
CSPD[‡]	22	Pneumonia-acute	58
Dehydration	23	Pneumonia-chronic	59
Dentition poor	24	Posterior v.c. Thrombus	60
Dermatophytosis	25	Pyelonephritis	61
DFA[**]	26	Recto-vaginal fistula	62
Endocarditis	28	Renal amyloidosis	63
Enteritis	29	Reticulitis	64
Enteropathy-chronic lymphocytic	30	Reticulitis traumatic	65
Foul in the foot	31	Ringworm	66
Fracture	32	Salmonellosis	67
Hepatic abscessation	33	Spastic paresis	68
Hydrocephalus	34	Tendons contracted	69
IBR[††]	35	Ulceration abomasal	70
Inferior prognathia	36	Urethral calculi	71
Johne's disease	37	Urethral rupture	72

[*]Bovine papular stomatitis; [†]Cerebro-cortical necrosis; [‡]Chronic suppurative pulmonary disease; [**]Diffuse fibrosing alveolitis; [‡‡]Malignant catarrhal fever.

Table 5-2 Representation of manual coding adopted for *post mortem* diagnoses from GUVS necropsy file.

Site	Code	Site	Code
Multi-system	0	Adrenal	25
Mouth	1	End. pancreas	26
Pharynx	2	Placenta	27
Oesophagus	3	Muscle	28
Forestomachs	4	Bones	29
Stomach	5	Joints	30
Small intestine	6	Tendons	31
Large intestine	7	Reproductive Male	32
Anus	8	Reproductive Female	33
Liver	9	Mammary glands	34
Exocrine pancreas	10	Prostate	35
Salivary glands	11	Kidney	36
Tonsil	12	Lower urinary	37
Upper respiratory	13	Blood and bone marrow	38
Lower respiratory	14	Thymus	39
Larynx	15	Spleen	40
Brain	16	Lymphatic	41
Spinal cord	17	Cardiovascular	42
Peripheral nerves	18	Skin	43
Autonomic NS	19	Connective tissues	44
Eye	20	Serosae	45
Ear	21	Septicaemia-toxaemia	46
Pituitary	22	Feet	47
Thyroid	23	Foetus	48
Parathyroid	24	Other	49

Table 5-3 Representation of coding developed by pathologists at GUVS to classify site of lesion at *post mortem* examination.

5.4.3 Excel spreadsheet functions

In order that the most accurate and efficient analysis be conducted, spreadsheet functions were exploited. The use of in-built spreadsheet functions to calculate the various probability measures and associated Biochemical Factors negated the necessity for manual calculations, and reduced errors associated with rounding and transcription. For correct calculation of the Biochemical Factor for each coded diagnosis or site, within each biochemistry parameter percentile band grouping, the spreadsheets for each parameter had to be carefully designed. The most important consideration in the construction of the spreadsheets was the information necessary to calculate the Biochemical Factor.

There were four basic approaches adopted for interrogation of the cattle data, namely, the investigation of diagnoses grouped within irregular biochemistry percentile

bands; diagnoses grouped within regular biochemistry percentile bands; sites grouped within irregular biochemistry percentile bands; and sites grouped within regular biochemistry percentile bands. For each of these approaches, a "directory" within the personal computer hard disk was created. Each biochemistry parameter selected for Biochemical Factor calculation was then allocated a separate Excel file within the appropriate directory. Each directory therefore contained 14 files. Using the biochemistry parameter albumin and the approach pertaining to diagnoses grouped within irregular percentile bands as an example, the design of the spreadsheets required for calculation of the Biochemical Factor is described.

The first spreadsheet within the file contained simply details of the albumin results and associated diagnoses. The columns contained the hospital number for each case; the albumin result, coded 1 to 10 according to percentile band grouping (Table 5-1); the diagnosis, coded according to Table 5-2; and the diagnosis in full text format. The data were ordered by the coded albumin result and then by the diagnosis code. Table 5-4 displays the first ten rows within the spreadsheet for illustration.

Column A Hosp_no	*Column B* Alb-1	*Column C* diag1-code	*Column D* PMdiag1
113870	1	6	Bladder-rupture
122190	1	10	Carcinoma-disseminated uterine
119206	1	24	Dentition poor
120816	1	29	Enteritis-allergic
113169	1	37	Johne's disease
121168	1	37	Johne's disease
129027	1	37	Johne's disease
129799	1	37	Johne's disease
130515	1	44	Mucosal disease
127268	1	52	Ostertagiasis

Table 5-4 An illustration of the first ten rows from the first spreadsheet within the file used to calculate the Biochemical Factor for diagnoses within irregular percentile band groupings for albumin.

The Excel spreadsheet function which allowed names to be allocated to ranges of data was then employed. A total of 11 cell ranges were named: the range of cells which included the diagnosis codes associated with albumin percentile band codes 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and the range of cells associated with any albumin percentile band, i.e. all of diagnosis codes in the spreadsheet. All of these 11 aforementioned named ranges

related to only one column - that containing the diagnosis codes, i.e. *Column C* of Table 5-4.

The second spreadsheet was more complex in design. For each percentile band grouping there was an associated list of diagnoses, given in full text in one column, and in coded form in the next. The subsequent columns contained functions for the calculation of total frequency of a particular diagnosis; the frequency of the diagnosis within the percentile band grouping; the probability of the percentile band, given the diagnosis [P(B|D)]; the probability of the percentile band grouping given that it was not the diagnosis [P(B|D')]; and the Biochemical Factor [P(B|D)/P(B|D')]. Table 5-5 shows a reduced version of the spreadsheet, detailing only the first four coded diagnoses within the first five biochemistry percentile groupings for illustrative purposes.

**Col. A Percentile Band	Col. B Diagnosis	Col. C Dg code	Col. D Total freq.	Col. E %ile* freq.	Col. F Pr(B|D)	Col. G Pr(B|D')	Col. H BF†
Min -- 1	Abscessation	2	22	0	0.000	0.016	0.0
	Actinobacillosis	3	4	0	0.000	0.015	0.0
	Arthritis	4	17	0	0.000	0.015	0.0
	Arthrogryphosis	5	3	0	0.000	0.015	0.0
(11)			(728)				
2 -- 5	Abscessation	2	22	2	0.091	0.033	2.8
	Actinobacillosis	3	4	0	0.000	0.035	0.0
	Arthritis	4	17	0	0.000	0.035	0.0
	Arthrogryphosis	5	3	0	0.000	0.034	0.0
(25)							
6 – 10	Abscessation	2	22	2	0.091	0.055	1.6
	Actinobacillosis	3	4	0	0.000	0.057	0.0
	Arthritis	4	17	2	0.118	0.055	2.1
	Arthrogryphosis	5	3	0	0.000	0.057	0.0
(41)							
11 -- 25	Abscessation	2	22	2	0.091	0.156	0.6
	Actinobacillosis	3	4	2	0.500	0.152	3.3
	Arthritis	4	17	1	0.059	0.156	0.4
	Arthrogryphosis	5	3	0	0.000	0.154	0.0
(112)							
26 – 50	Abscessation	2	22	9	0.409	0.259	1.6
	Actinobacillosis	3	4	2	0.500	0.262	1.9
	Arthritis	4	17	8	0.471	0.259	1.8
	Arthrogryphosis	5	3	0	0.000	0.265	0.0
(192)							

**Column; *Percentile; †Biochemical Factor

Table 5-5 A reduced version of the spreadsheet used to calculate the Biochemical Factor, with albumin given as an example. The first four coded diagnoses within the first five biochemistry percentile bands are given for illustration.

The results in Table 5-5 may be further explained by describing the functions from which they were derived. The "Total Frequency", *Column D*, reflected the total number of cases out of all of those which had albumin measured which had the diagnosis code detailed in the previous column, *Column C*. For example, arthritis was the diagnosis for a total of 17 cases. The formula which was used to determine this for each diagnosis is shown in Excel Function 5.1.

=COUNTIF(allalb,C*R*)
Where "allalb" was the named cell range which referred to all diagnoses with any albumin result; and C*R* was a direct cell reference to the diagnosis code, with C reflecting *Column C* which contained all the diagnosis codes, and *R* reflecting the row number within the spreadsheet which pertained to the diagnosis.

Excel Function 5.1 Function used to calculate the frequency of each of the coded *post mortem* diagnoses within all the cattle cases which had albumin measured.

The "percentile frequency", given in *Column E* of Table 5-5, represented the number of cases which had an albumin result within a given percentile band and which had the diagnosis detailed in *Column C*. For example, given that the albumin result lay in the 6-10 percentile band, there were two cases of arthritis. The formula used to calculate the percentile frequency is given in Excel Function 5.2.

=COUNTIF(alb*n*,C*R*)
Where "alb*n*" was the named cell range which referred to the set of coded diagnoses which had an albumin result which lay in the n^{th} percentile band grouping; and C*R* was a direct cell reference to the diagnosis code, with C reflecting *Column C* which contained all the diagnosis codes, and *R* reflecting the row number within the spreadsheet which pertained to the diagnosis.

Excel Function 5.2 Function used to calculate the frequency of each of the coded *post mortem* diagnoses, given that the albumin result lay in the n^{th} percentile band grouping.

P(B|D), shown in *Column F* of Table 5-5, represented the probability of the albumin result falling within a particular percentile band, given a particular diagnosis, and was calculated by dividing the number of cases of the disease in the given percentile band by

the total number of cases of the disease. Excel Function 5.3 shows how this probability measure was calculated for each diagnosis within each percentile band.

=E*R*/D*R*
Where E refers to *Column E*, which contained the frequency of a diagnosis within a given percentile band grouping; D referred to *Column D*, which contained the total frequency of a diagnosis; and *R* represented the row within the spreadsheet which referred to the diagnosis code.

Excel Function 5.3 Function used to calculate the probability of an albumin result falling within a particular percentile band, given a particular diagnosis, P(B|D).

For the remainder of the probabilities to be calculated, additional information was required. This included the total number of cases which had albumin measured, and the number of cases within each percentile band grouping. These were simply calculated using the named cell ranges for each group, detailed within the first spreadsheet. In *Column D, Row 5* of Table 5-5, the bracketed number, 728, was the total number of cases which had albumin measured. For some of the diagnoses, no coding had been allocated (5.4.2), even though albumin had been measured. However, it was important for the accurate computation of the probability measures that such cases be included for analysis and therefore blank diagnosis code cells associated with an albumin result had to be included for calculation. Excel Function 5.4 was used for this calculation.

=COUNT(allalb)+COUNTBLANK(allalb)
Where "allalb" was the named cell range which referred to all diagnoses with any albumin result.

Excel Function 5.4 Function used to calculate the total number of cases which had albumin measured, based on named cell ranges within a spreadsheet.

The result of the computation shown in Excel Function 5.4 was stored in a particular locked cell within the spreadsheet, namely, cell in *Column D, Row 72*. The reference to this cell was D72.

In *Column A, Rows 5, 10, 15, 20 and 25* of Table 5-5, the bracketed numbers 11, 25, 41, 112 and 192 reflect the number of cases for which the albumin result had fallen within the min-1, 2-5, 6-10, 11-25, and 26-50 percentile bands, respectively. Again, due to the fact that not all diagnoses were coded, some blank cells had to be counted to give a true indication of the number of cases within each group. Excel Function 5.5 was used to calculate the frequencies for each percentile band.

=COUNT(alb*n*)+COUNTBLANK(alb*n*)
Where "alb*n*" was the named cell range which referred to the set of diagnoses which had an albumin result which lay in the n^{th} percentile band

Excel Function 5.5 Function used to calculate the total number of cases which an albumin value which fell within percentile band, *n*.

Particular locked cells within the spreadsheet were used to store the results for the frequency of cases with an albumin result falling within a particular percentile band generated using Excel Function 5.4. These cells were *Column A, Row 72; Column A Row 143; Column A, Row 214; Column A, Row 285; Column A, Row 356; Column A, Row 427; Column A, Row 498; Column A, Row 569; Column A, Row 640 and Column A, Row 711*; representing the number of cases within an albumin result within the min-1; 2-5; 6-10; 11-25; 26-50; 51-75; 76-90; 91-95; 96-99 and 99-max percentile band groupings respectively. The cell references were represented as A72; A143; A214; A285; A356; A427; A498; A569; A640; and A711, respectively.

Pr(B|D'), shown in *Column G* of Table 5-5, which represented the probability of the percentile band grouping given that it was not the diagnosis, was then simply calculated using the Excel Function 5.6. Excel Function 5.6 shows the calculation for the first percentile grouping, for illustration.

=(A72-E*R*)/(D72-D*R*)
Where, A72 was a cell reference to the number of cases which had an albumin result within the first percentile band; E*R* was the number of cases which had diagnosis code relating to *Row R* and had an albumin result which fell in the first percentile band; D72 was a cell reference to the total number of cases which had albumin measured; and D*R* was the total number of cases which had diagnosis code relating to *Row R*.

Excel Function 5.6 Function used to calculate the probability of an albumin result falling within a percentile band min-1, given that it was not the particular diagnosis.

With the calculations for *Columns F* and *G* of Table 5-5 complete, it was then simple to compute the Biochemical Factor, given in *Column H*, for each coded diagnosis within each percentile band by dividing *Column F* by *Column G*, as shown in Excel Function 5.7.

=F*R*/G*R*
Where F*R* refers to the probability of an albumin result falling within a particular percentile band, given a particular diagnosis code in *Row R*; and GR refers to the probability of an albumin result falling within a particular percentile band, given that it was not the particular diagnosis code in *Row R*.

Excel Function 5.7 Function used to calculate the Biochemical Factor for each diagnosis within each percentile band.

If the results for the results for the various frequency and probability measures were calculated individually for each diagnosis within each percentile band for each clinical biochemistry parameter, the process would have been very time-consuming. A generic template spreadsheet was therefore constructed.

The template contained all the necessary columns and functions, as described for the example of albumin above. In those cases where a reference to a named cell range, such as "allalb", was required; the code for the biochemistry parameter was replaced with "XXX". That is, on each occasion that "alb" appeared for albumin, "XXX" appeared in the generic template. The first spreadsheet for each biochemistry parameter was created as described for albumin, and the appropriate cell ranges named using logical biochemistry parameter codes, e.g. "glob" for globulin. The generic template required for the calculation of the Biochemical Factor was then imported to the biochemistry

parameter's file. Due to the fact that, on import, the names within the generic template, such as "allXXX", were not recognised by the spreadsheet, the term "#NAME?" appeared in each cell whose formula contained a reference. By employing the automatic replacement spreadsheet function, all instances of "XXX" were replaced with the biochemistry code name, such as "glob" for globulin. Consequently, the calculations within the spreadsheet were completed virtually instantaneously.

Although the initial development of the spreadsheets within the files for each biochemistry parameter was time-consuming, the ultimate achievement was a means by which the Biochemical Factors could be calculated within minutes.

5.5 RESULTS

A total of 1096 cattle were identified as suitable for inclusion in the study, because they had biochemistry testing carried out as part of their investigation at GUVS during the period 1988 to July 1997. The percentile analysis techniques were first carried out on all the data, to allow the data generated from different analysers to be combined. The 1096 animals was then divided into two unequal sets - the training dataset, and the test dataset. The probability calculations to determine the Biochemical Factor for each diagnosis within each percentile band were calculated using only the training dataset, as discussed in 5.3.3. The training set consisted of 746 cases, randomly selected from the total of 1096.

5.5.1 Summary statistics

For the 1096 cases, Table 5-6 shows the frequency with which plasma biochemistry samples were taken. The majority (61%) of cases had only one biochemistry panel taken, within which a number of different biochemistry parameters were measured. The range of the number of biochemistry samples taken from an individual animal was from 1 to 13. The mean number of biochemistry samples taken per cow was 1.8, and the median was 1.

No. of samples taken per cow	Frequency
1	667
2	248
3	82
4	43
5	23
6	10
7	7
8	9
9	4
10	1
10+	2

Table 5-6 Breakdown of the number of biochemistry samples taken for a total of 1096 cattle cases which presented to the University of Glasgow Veterinary School between the period of 1988 to July 1997.

Table 5-7 shows the number of times each biochemistry parameter was measured within a selected panel. It can be seen that urea, then total protein, albumin and globulin were measured most often, in almost 98% of cases, with individual parameter selection reducing in frequency down to glucose, which was measured least often, in only 20 of the 1096 cases. A core of 14 parameters were measured in most cases, namely, urea, total protein, albumin, globulin, potassium, sodium, chloride, alkaline phosphatase, calcium, magnesium, phosphate, aspartate amino-transferase, bilirubin and creatinine. Further analysis focused on the core of 14 parameters.

Biochemistry parameter	Frequency
Urea	1076
Total protein	1073
Albumin	1073
Globulin	1073
Potassium	1063
Sodium	1062
Chloride	1062
Alkaline Phosphatase	1057
Calcium	1035
Magnesium	1023
Phosphate	1012
Aspartate amino-transferase	998
Bilirubin	970
Creatinine	947
γ-glutamyl-transferase	847
Cholesterol	620
Creatinine phosphokinase	63
Glucose	20

Table 5-7 Parameter selection frequency within a panel of plasma biochemistry tests collected from 1096 cattle cases seen at University of Glasgow Veterinary School over a period of approximately eight years.

5.5.2 Biochemistry parameter distributions

The distributions of the data generated from the biochemistry analyser which was used for the longest time during the study period were investigated, that is, the results pertaining to the COBAS-MIRA Biochemistry Analyser (Appendix VII). Investigation of the biochemistry parameters using histograms which displayed the distribution of results suggested that none of the parameters conformed to a normal distribution. For example, Figure 5-1 demonstrates that the distribution of urea was skew with a long tail to the right and Figure 5-2 shows the distribution of the sodium results was skew with a tail to the left. Most parameters displayed skew distributions with a tail to the right, but in the cases of sodium, chloride and calcium there was a slight tail to the left.

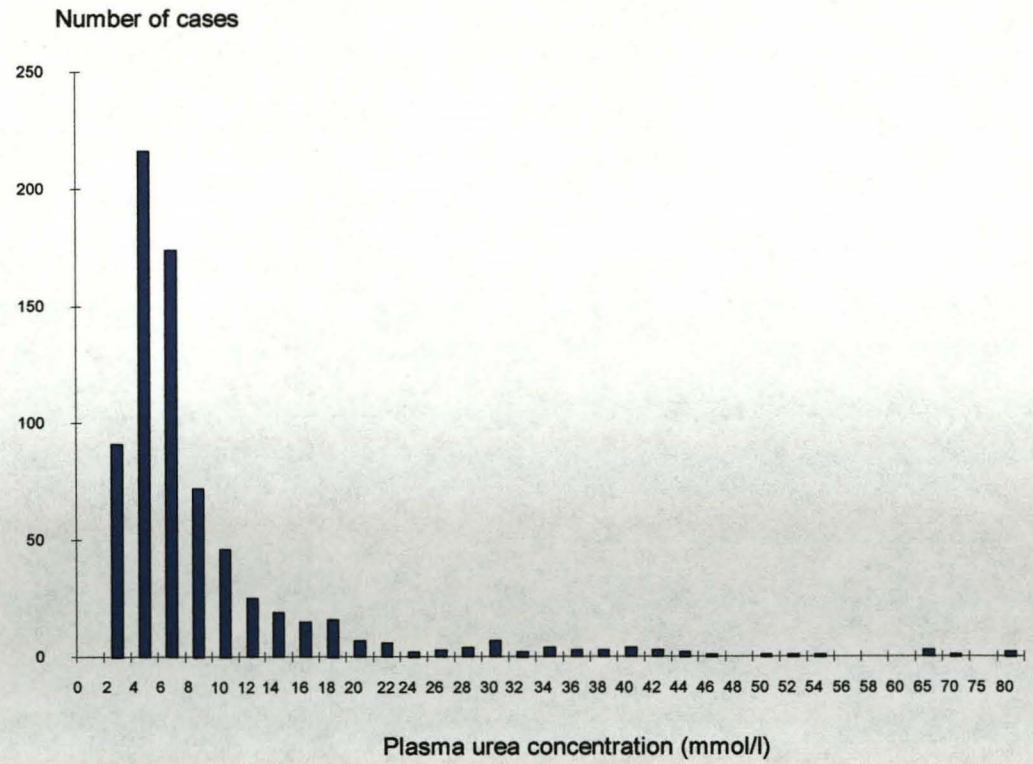


Figure 5-1 Distribution of plasma urea results (mmol/l) from cattle referral cases seen at GUVS over the period of the study.

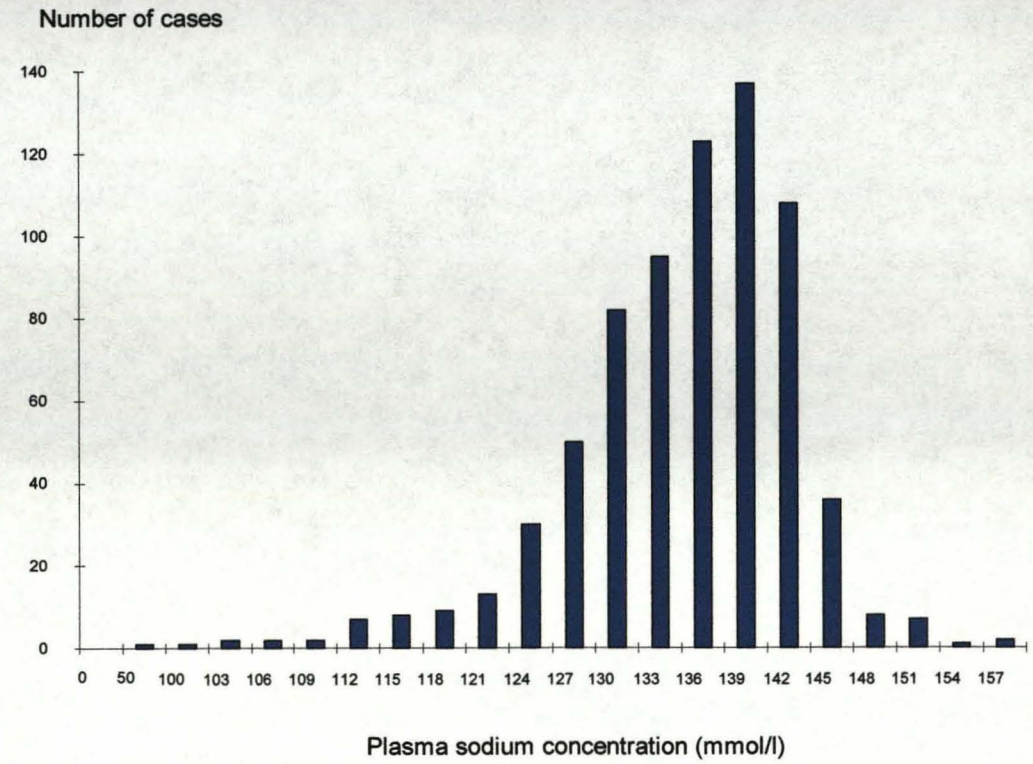


Figure 5-2 Distribution of plasma sodium results (mmol/l) from cattle referral cases seen at GUVS over the period of the study.

Table 5-8 shows the descriptive statistic summaries for plasma urea and sodium. Positive kurtosis indicated a peaked distribution whereas negative kurtosis indicated a flat distribution. Skewness characterised the degree of asymmetry of a distribution around its mean.

	Biochemistry Parameter	
Statistic	Albumin	Sodium
Mean	7.813	133.7
Standard Error	0.386	0.3
Median	4.49	135
Mode	3.65	138
Standard Deviation	10.461	8.4
Kurtosis	28.39	21.01
Skewness	4.40	-2.57
Range	119.13	115
Minimum	0.87	41
Maximum	120.00	156

Table 5-8 Descriptive statistics for plasma albumin and sodium results from cattle referral cases seen at GUVS over study period.

In keeping with the graphical presentations of the data, the skewness for the plasma urea data was positive, while that for the plasma sodium results was negative. The kurtosis and skewness statistics varied depending on the parameter, but none of the parameters was classified as being normally distributed. The majority of parameters had positive skewness, indicative of a tail to the right. However, sodium, chloride and calcium had negative skewness, that is, had tails to the left. The descriptive statistics for each of the biochemistry parameters are listed in Appendix III.

5.5.3 Percentile analysis

Tables 5-9 and 5-10 give the results achieved for the percentile analysis of the biochemistry data which were generated using the COBAS-MIRA Biochemistry Analyser, displaying the results for the irregular percentile and the regular percentile approaches, respectively. Similarly, Tables 5-11 and 5-12 show the results achieved for the percentile analysis of the biochemistry data which were generated using the AXON Biochemistry Analyser, displaying the results for the irregular percentile and the regular

percentile approaches, respectively. The AXON Biochemistry Analyser was in use at GUVS at the time of writing of this thesis.

The percentile values in Tables 5-9, 5-10, 5-11 and 5-12 were used to assess parameter values. Using Table 5-11 for illustration, because it reflects the results generated from the biochemistry analyser currently in use at GUVS, interpretation is discussed. For example, a plasma creatinine value of 140 μmol/l fell within the 75th to the 90th percentile band, and could be described as slightly raised; a value of 1200 μmol/l fell within the 99th to the maximum percentile band, and could be classified as extremely high because only 1% of the cattle which presented to GUVS over the two year period the AXON Biochemistry Analyser was used had such high values. Table 5-11, therefore, was used to evaluate the degree of abnormality of a value from the defined population of cattle presenting to GUVS.

Parameter	Units	Min	Percentile 1%	5%	10%	25%	50%	75%	90%	95%	99%	Max
Urea	mmol/l	0.870	1.040	1.400	1.854	2.855	4.490	7.955	16.250	28.811	52.682	120.000
Sodium	mmol/l	41.0	109.2	120.2	124.0	130.0	135.0	139.0	142.0	143.9	149.0	156.0
Potassium	mmol/l	1.00	1.70	2.72	3.20	3.70	4.20	4.80	5.50	6.08	7.60	23.00
Chloride	mmol/l	49.0	60.0	79.0	84.0	90.0	96.0	100.0	103.0	106.0	111.0	126.0
Calcium	mmol/l	1.200	1.680	1.960	2.020	2.190	2.350	2.490	2.630	2.710	2.870	3.340
Magnesium	mmol/l	0.140	0.279	0.416	0.460	0.530	0.650	0.770	0.880	0.984	1.620	2.500
Phosphate	mmol/l	0.250	0.818	1.120	1.320	1.680	2.040	2.410	2.908	3.476	5.198	7.380
Creatinine	µmol/l	43.0	55.1	65.0	72.0	85.0	105.0	137.0	196.2	291.2	1072.8	6195.0
Bilirubin	µmol/l	0.0	0.0	0.0	0.0	1.0	2.0	8.0	16.0	22.0	43.4	86.0
AP	U/l	30.0	42.0	58.6	71.1	106.0	154.0	251.3	398.4	509.8	802.0	1455.0
AST	U/l	8.0	25.4	41.0	47.0	63.0	87.0	141.0	249.0	354.0	769.4	2298.0
Total protein	g/l	4.0	46.0	55.0	61.0	68.0	78.0	88.0	100.0	106.0	115.7	125.0
Albumin	g/l	2.0	15.0	18.0	20.0	24.0	28.0	32.0	36.0	38.0	43.0	60.0
Globulin	g/l	2.0	19.4	27.0	31.0	39.0	48.0	60.0	72.5	81.0	93.0	101.0

Table 5-9 Results of percentile analysis performed on each of the biochemistry parameters investigated, for data generated using the COBAS-MIRA biochemistry analyser. The use of the COBAS-MIRA biochemistry analyser at GUVS was stopped on 28/02/95. Results are based on a maximum of 752 cattle referral cases seen at GUVS over the period of the study. Irregular percentile groupings are shown.

Parameter	Units	Min	Percentile 10%	20%	30%	40%	50%	60%	70%	80%	90%	Max
Urea	mmol/l	0.870	1.854	2.558	3.272	3.910	4.490	5.278	6.828	9.294	16.250	120.000
Sodium	mmol/l	41.0	124.0	128.0	131.0	133.0	135.0	137.0	138.0	140.0	142.0	156.0
Potassium	mmol/l	1.00	3.20	3.60	3.80	4.00	4.20	4.40	4.60	5.00	5.50	23.00
Chloride	mmol/l	49.0	84.0	88.0	92.0	94.0	96.0	98.0	99.0	101.0	103.0	126.0
Calcium	mmol/l	1.200	2.020	2.130	2.230	2.290	2.350	2.400	2.453	2.522	2.630	3.340
Magnesium	mmol/l	0.140	0.460	0.514	0.560	0.608	0.650	0.690	0.744	0.800	0.880	2.500
Phosphate	mmol/l	0.250	1.320	1.582	1.740	1.924	2.040	2.176	2.322	2.510	2.908	7.380
Creatinine	µmol/l	43.0	72.0	80.0	90.0	97.0	105.0	115.0	128.0	148.0	196.2	6195.0
Bilirubin	µmol/l	0.0	0.0	1.0	1.0	2.0	2.0	4.0	6.0	10.0	16.0	86.0
AP	U/l	30.0	71.1	96.0	112.3	130.4	154.0	187.6	227.0	280.0	398.4	1455.0
AST	U/l	8.0	47.0	59.0	67.0	75.0	87.0	103.0	124.0	166.0	249.0	2298.0
Total protein	g/l	4.0	61.0	66.0	70.0	73.0	78.0	81.0	85.0	90.0	100.0	125.0
Albumin	g/l	2.0	20.0	23.0	25.0	27.0	28.0	30.0	32.0	33.0	36.0	60.0
Globulin	g/l	2.0	31.0	36.0	40.0	43.0	48.0	52.0	57.0	64.0	72.5	101.0

Table 5-10 Results of percentile analysis performed on each of the biochemistry parameters investigated, for data generated using the COBAS-MIRA biochemistry analyser. The use of the COBAS-MIRA biochemistry analyser at GUVS was stopped on 28/02/95. Results are based on a maximum of 752 cattle referral cases seen at GUVS over the period of the study. Regular percentile groupings are shown.

Parameter	Units	Min	Percentile 1%	5%	10%	25%	50%	75%	90%	95%	99%	Max
Urea	mmol/l	0.90	1.00	1.51	1.90	3.00	4.40	7.08	13.05	18.66	41.92	102.60
Sodium	mmol/l	108.0	118.8	122.9	126.8	131.0	136.0	138.0	141.0	142.0	145.0	151.0
Potassium	mmol/l	1.80	2.33	2.80	3.20	3.70	4.10	4.60	5.10	5.81	7.77	13.40
Chloride	mmol/l	58.0	65.0	84.0	88.0	94.0	98.0	102.0	105.0	107.0	111.0	118.0
Calcium	mmol/l	1.020	1.538	1.840	1.980	2.110	2.260	2.430	2.580	2.695	2.843	3.010
Magnesium	mmol/l	0.320	0.394	0.480	0.530	0.610	0.740	0.840	0.940	1.040	1.274	1.500
Phosphate	mmol/l	0.330	0.835	1.218	1.422	1.720	2.050	2.480	2.838	3.150	4.372	5.730
Creatinine	µmol/l	51.0	59.8	65.9	69.0	84.0	104.0	134.0	169.2	239.8	436.8	2050.0
Bilirubin	µmol/l	0.0	0.0	1.0	1.0	2.0	3.0	8.0	17.0	25.3	57.3	109.0
AP	U/l	35.0	50.3	71.3	87.0	120.0	173.0	277.0	461.4	595.1	834.8	1802.0
AST	U/l	25.0	27.7	39.0	43.0	58.0	81.0	122.5	212.6	352.0	821.7	2040.0
Total protein	g/l	39.0	47.3	53.0	56.0	63.0	70.0	77.0	88.0	93.4	108.4	122.0
Albumin	g/l	16.0	19.0	20.9	22.0	26.3	31.0	35.0	39.0	40.0	44.2	51.0
Globulin	g/l	13.0	19.0	22.0	25.7	31.0	38.0	47.0	56.3	66.0	86.2	98.0

Table 5-11 Results of percentile analysis performed on each of the biochemistry parameters investigated, for data generated using the AXON biochemistry analyser. The AXON biochemistry analyser was in use at GUVS at the time of writing (11/97). Results are based on a maximum of 285 cattle referral cases seen at GUVS over the period of the study. Irregular percentile groupings are shown.

Parameter	Units	Min	Percentile 10%	20%	30%	40%	50%	60%	70%	80%	90%	Max
Urea	mmol/l	0.90	1.90	2.50	3.30	3.80	4.40	5.30	6.30	8.30	13.05	102.60
Sodium	mmol/l	108.0	126.8	130.0	132.0	134.0	136.0	137.0	137.0	139.0	141.0	151.0
Potassium	mmol/l	1.80	3.20	3.56	3.80	4.00	4.10	4.30	4.50	4.70	5.10	13.40
Chloride	mmol/l	58.0	88.0	92.0	95.0	96.0	98.0	99.0	101.0	102.8	105.0	118.0
Calcium	mmol/l	1.020	1.980	2.080	2.160	2.230	2.260	2.320	2.385	2.460	2.580	3.010
Magnesium	mmol/l	0.320	0.530	0.584	0.640	0.680	0.740	0.780	0.824	0.860	0.940	1.500
Phosphate	mmol/l	0.330	1.422	1.592	1.800	1.934	2.050	2.210	2.374	2.558	2.838	5.730
Creatinine	µmol/l	51.0	69.0	80.0	87.4	93.0	104.0	113.0	125.0	144.0	169.2	2050.0
Bilirubin	µmol/l	0.0	1.0	1.0	2.0	3.0	3.0	4.0	7.0	9.0	17.0	109.0
AP	U/l	35.0	87.0	112.2	128.4	151.0	173.0	207.6	247.0	306.4	461.4	1802.0
AST	U/l	25.0	43.0	56.0	62.0	71.0	81.0	94.6	113.0	139.8	212.6	2040.0
Total protein	g/l	39.0	56.0	60.0	64.0	66.8	70.0	73.0	75.0	81.0	88.0	122.0
Albumin	g/l	16.0	22.0	25.0	28.0	30.0	31.0	32.0	34.0	36.0	39.0	51.0
Globulin	g/l	13.0	25.7	30.0	33.0	36.0	38.0	41.0	45.0	50.0	56.3	98.0

Table 5-12 Results of percentile analysis performed on each of the biochemistry parameters investigated, for data generated using the AXON biochemistry analyser. The AXON biochemistry analyser was in use at GUVS at the time of writing (11/97). Results are based on a maximum of 285 cattle referral cases seen at GUVS over the period of the study. Regular percentile groupings are shown.

5.5.4 Differential diagnoses

Table 5-13 shows the frequency of the ten most common *post mortem* diagnoses which were obtained for all those cattle cases which had any plasma biochemistry testing carried out as part of their investigation. Mucosal disease appeared most commonly, then chronic suppurative pulmonary disease, and so on to posterior vena caval thrombus. Similar disease frequency breakdown tables were constructed within each individual biochemistry parameter measured. Slight variations in these parameter specific disease breakdown tables may have reflected the biochemistry parameter selection bias arising due to the clinician's prior knowledge from the historical and clinical presentation of a case.

Diagnosis	Frequency
Mucosal disease	87
CSPD*	75
Johne's disease	47
Endocarditis	44
Lymphosarcoma	40
Traumatic pericarditis	34
Chronic pneumonia	33
Congenital cardiac defect	30
Abscessation	27
Arthritis	27
Posterior vena caval thrombus	21

*Chronic suppurative pulmonary disease

Table 5-13 The frequency of the ten most common *post mortem* diagnoses, for 1096 cattle cases which had plasma biochemistry testing carried out as part of their investigation at the University of Glasgow Veterinary School, between 1988 and 1997.

5.5.5 Biochemical Factor

Following the summaries for the entire dataset, the percentile analysis, and recombining of all the data generated from each of the three Biochemistry Analysers, a random sample of 746 animals was selected for the calculation of the Biochemical Factor. The Biochemical Factor was calculated using four separate approaches: diagnoses within irregular percentile groupings; diagnoses within regular percentile groupings; pathological sites within irregular percentile groupings; and pathological sites within regular percentile band groupings. Each of these approaches is illustrated using the

example of the biochemistry parameter urea. The tables for each of the other parameters are shown in Appendix IV.

5.5.5.1 Diagnoses within irregular percentile groupings

Table 5-14 gives the results of the *post mortem* diagnosis grouped within irregular percentile bands for plasma urea, with the corresponding Biochemical Factors. The highest Biochemical Factors were apparent in the outermost percentile bands, confirming the clinical perspective that most information value from measuring urea was achieved when values were markedly raised or lowered. Tables constructed for each of the biochemistry parameters revealed a similar pattern, namely, high Biochemical Factors within the uppermost percentile bands, reducing to low values (1 or 2) within the middle percentile bands, and increasing again towards the lowermost percentile bands (Appendix IV). The tabulation and ranking of the *post mortem* diagnoses, within each percentile band for each biochemistry parameter provided an indication of the most likely diseases associated with particular biochemistry results. Using an example of urea of 30 mmol/l which lay in the top 5% of all the hospital case results, one of the most likely diseases was pyelonephritis. To further aid with decision support, the Biochemical Factor indicated how many times more likely the disease was to be pyelonephritis, than before the biochemistry information had been available. In this case, given that the urea value was 30 mmol/l, the cow was 5.8 times more likely to have pyelonephritis than before the test result was available. Interestingly, if the urea value was 70 mmol/l, then pyelonephritis was 28.8 times more likely.

5.5.5.2 Diagnoses within regular percentile groupings

Table 5-15 shows the results of the *post mortem* diagnoses grouped within regular percentile bands for plasma urea, and the corresponding Biochemical Factors. Similar to the pattern for the diagnoses grouped within the irregular percentile bands, the differential diagnosis list was different within each percentile band, indicating that knowledge of biochemistry information altered the likelihood of different diagnoses. For example, in the 51st to 70th percentile band, the most common diagnoses included mucosal disease, chronic suppurative pulmonary disease and Johne's disease. Each of these diagnoses were among the most common diagnoses made, irrespective of biochemistry result (Table 5-13). However, in the 90th to maximum percentile band, the

most common diagnoses included mucosal disease, lymphosarcoma and pyelonephritis. It was particularly interesting that pyelonephritis featured within this list due to the fact that out of the approximately 80 cases within that band, it was the third most common despite the fact that it did not appear on the list of the ten most common diagnoses in the database (Table 5-13). The associated Biochemical Factors for each diagnosis also gave an indication of how many times more likely the diagnosis was, given the urea biochemistry information. For example, pyelonephritis was 4.4 times more likely if the urea value lay within the top 10% of results achieved.

5.5.5.3 Sites within irregular percentile groupings

Table 5-16 indicates the ten most common pathological sites in which the primary lesion lay for those 1096 cases which had biochemistry testing carried out as part of their investigation at GUVS. Lower respiratory and cardiovascular were by far the most common sites affected.

Table 5-17 shows the grouping of pathological sites within each irregular percentile band. Cardiovascular and lower respiratory sites appeared in the majority of percentile bands. However, on each occasion that cardiovascular or lower respiratory appeared, the Biochemical Factor was only 1 or 2, indicating little change in likelihood of the disease based on the biochemistry information. In contrast, kidney and lower urinary sites were both present in the 99th to maximum percentile band, with very high associated Biochemical Factors of 16.8 and 41.4, respectively.

Site	Frequency
Lower respiratory	159
Cardiovascular	156
Small intestine	86
Multi-system	72
Mouth	45
Joints	38
Bones	37
Kidney	29
Forestomachs	27
Stomach	26

Table 5-16 The frequency of the ten most common pathological sites, for those cattle cases which had plasma biochemistry testing carried out as part of their investigation at the University of Glasgow Veterinary School, between 1988 and 1997.

Percentile Band	Most frequent diagnoses	Biochemical Factor
Min - 1	CSPD*	4.4
2 - 5	Abscessation	5.2
	Arthritis	3.1
	CSPD	1.0
	Endocarditis	1.8
6 - 10	Johne's disease	2.6
	Ostertagiasis	6.9
11 - 25	CSPD	1.2
	Mucosal disease	0.7
	Pneumonia-chronic	2.1
	Abscessation	1.6
	Osteomyelitis	4.5
26 - 50	CSPD	1.0
	Mucosal disease	0.8
	Johne's disease	1.2
	Endocarditis	1.2
	Pericarditis traumatic	1.2
	Pneumonia-chronic	1.3
51 - 75	Mucosal disease	1.2
	CSPD	1.1
	Johne's disease	1.2
	Abscessation	1.6
	Lymphosarcoma	1.2
76 - 90	Mucosal disease	1.3
	Congenital cardiac defect	3.0
	CSPD	1.1
	Endocarditis	1.6
91 - 95	Mucosal disease	2.0
	Lymphosarcoma	3.4
	Cardiomyopathy	8.8
	Endocarditis	1.5
	Enteritis	8.8
96 - 98	Mucosal disease	3.5
	Johne's disease	2.7
	Pericarditis traumatic	2.7
	Peritonitis	7.2
	Pyelonephritis	5.8
99 - max.	Pyelonephritis	28.8

*Chronic suppurative pulmonary disease

Table 5-14 Biochemical Factor calculated for the most common diagnoses within each irregular percentile band for urea, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile Band	Most frequent diagnoses	Biochemical Factor
Min - 10	CSPD*	1.2
	Abscessation	2.3
	Arthritis	2.4
	Johne's disease	1.2
11 - 20	CSPD	1.7
	Abscessation	2.4
	Mucosal disease	0.7
21 - 30	Lymphosarcoma	1.9
	Pneumonia-chronic	2.7
	Endocarditis	1.4
	Mucosal disease	0.7
	Reticulitis traumatic	3.9
31 - 40	Johne's disease	1.7
	CSPD	0.9
	Endocarditis	1.2
	Mucosal disease	0.6
	Pericarditis traumatic	1.7
41 - 50	CSPD	1.8
	Mucosal disease	1.0
	Endocarditis	1.3
	Fracture	5.7
	Johne's disease	1.2
51 - 60	CSPD	1.3
	Mucosal disease	1.2
	Abscessation	2.2
	Congenital cardiac defect	1.7
	Johne's disease	1.2
61 - 70	Mucosal disease	1.3
	CSPD	1.0
	Johne's disease	1.3
	Lymphosarcoma	1.2
	Pericarditis traumatic	1.5
71 - 80	Congenital cardiac defect	2.9
	Mucosal disease	1.1
	CSPD	1.0
	Lymphosarcoma	1.5
81 - 90	Mucosal disease	1.3
	Endocarditis	2.2
	Congenital cardiac defect	2.3
91 - max.	Mucosal disease	2.3
	Lymphosarcoma	1.6
	Pyelonephritis	4.4

*Chronic suppurative pulmonary disease

Table 5-15 Biochemical Factor calculated for the most common diagnoses within each regular percentile band for urea, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile Band	Most frequent sites	Biochemical Factor
Min - 1	Lower respiratory	2.0
2 - 5	Lower respiratory	1.2
	Joints	3.4
	Liver	3.5
	Cardiovascular	0.4
	Connective tissues	7.7
6 - 10	Lower respiratory	1.3
	Small intestine	1.5
11 - 25	Lower respiratory	1.4
	Cardiovascular	0.8
	Bones	1.9
	Small intestine	0.9
	Skin	3.3
26 - 50	Lower respiratory	1.2
	Cardiovascular	1.1
	Small intestine	1.0
	Mouth	1.2
	Bones	1.1
51 - 75	Cardiovascular	0.9
	Lower respiratory	0.8
	Multi-system	1.7
	Small intestine	1.1
	Mouth	1.3
76 - 90	Cardiovascular	1.7
	Lower respiratory	0.7
	Multi-system	1.6
	Forestomachs	1.8
	Small intestine	0.6
91 - 95	Cardiovascular	1.2
	Multi-system	1.4
	Small intestine	0.8
96 - 99	Small intestine	3.7
	Cardiovascular	1.0
	Kidney	5.3
	Multi-system	1.2
	Serosae	3.6
99 - max.	Lower respiratory	2.4
	Kidney	16.8
	Lower urinary	41.4

Table 5-17 Biochemical Factor calculated for the most common pathological sites within each irregular percentile band for urea, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile Band	Most frequent sites	Biochemical Factor
Min - 10	Lower respiratory	1.4
	Joints	3.0
	Cardiovascular	0.5
	Small intestine	0.9
11 - 20	Lower respiratory	1.7
	Small intestine	1.4
	Cardiovascular	0.6
	Bones	2.1
21 - 30	Cardiovascular	1.0
	Lower respiratory	0.9
	Multi-system	1.1
	Bones	1.4
	Thymus	2.3
31 - 40	Cardiovascular	1.3
	Lower respiratory	1.1
	Small intestine	1.2
	Mouth	1.1
41 - 50	Lower respiratory	1.4
	Cardiovascular	1.0
	Small intestine	1.3
	Bones	1.6
51 - 60	Cardiovascular	1.0
	Lower respiratory	0.9
	Multi-system	2.0
	Small intestine	1.1
61 - 70	Lower respiratory	0.9
	Multi-system	1.4
	Mouth	2.0
	Small intestine	1.2
71 - 80	Cardiovascular	1.4
	Lower respiratory	0.7
	Multi-system	1.6
	Forestomachs	2.4
81 - 90	Cardiovascular	2.1
	Multi-system	1.7
	Lower respiratory	0.7
91 - max.	Cardiovascular	1.0
	Small intestine	1.7
	Kidney	4.0
	Multi-system	1.2
	Lower respiratory	0.5
	Lower urinary	4.7

Table 5-18 Biochemical Factor calculated for the most common pathological sites within each regular percentile band for urea, based on data from cattle cases presented to the University of Glasgow Veterinary School.

5.5.5.4 Sites within regular percentile groupings

Table 5-18 shows the grouping of pathological sites within each regular percentile band. In a pattern similar to that for the irregular percentile groupings, the most common sites appeared within several of the percentile bands, but were in each case associated with Biochemical Factors of 1 or 2. However, the only percentile band in which kidney and lower urinary appeared was that associated with the top 10% of urea values. The Biochemical Factors of 4.0 and 4.7 indicated that these sites were much more likely given the high urea values.

The example of pyelonephritis and of the kidney which was highlighted in each of the percentile grouping approaches emphasised the increased information value of clinical biochemistry testing which may be achieved by adoption of a new approach to interpretation. Assessment of urea in cattle was particularly suited to this means of interpretation because dietary factors may influence the result, and the approach of the reference range offered no further guidance in this respect.

5.6 DISCUSSION

As both human and veterinary medicines advance, so too do clients' expectations. Clients demand a diagnosis, explanations of disease processes and treatment, and a prognosis. These criteria, realistically, may never be met for every case, but as an ever increasing range of ancillary clinical tests becomes readily available to the clinician, the chances of reaching a diagnosis are heightened. In this respect, an extensive array of biochemical tests is now available to most practising veterinary clinicians. However, access to such results are in vain, if they are inappropriately interpreted. Chapters 4 and 5 have examined the potential of data contained within a hospital database to provide useful knowledge, which may be ultimately used to assist in the interpretation of clinical biochemistry data.

5.6.1 Reference ranges

Currently, the standard guide to the interpretation of clinical biochemistry results is based on the "reference range" for a parameter (Okotie-Eboh *et al.*, 1992; Jensen and Høier, 1993; Mbassa and Poulsen, 1993a; Mee, 1995; Mee and McLaughlin, 1995; Hicks *et al.*, 1995). The concept of reference values was introduced to human medicine in the 1960's

(Gräsbeck, 1990; Fraser and Peterson, 1993). A reference interval represents a range of values within which the result for an animal from a defined population would be expected (MacWilliams and Thomas, 1992). Any result outwith these values is broadly classified as abnormally lowered or raised (Jensen and Høier, 1993).

The reference range for a biochemistry parameter is usually calculated in one of three ways, commonly based on a sample from a population of "healthy" animals. First, if the distribution of the results obtained in the healthy population is normal, then mean and standard deviation statistics are calculated, and the range is determined by the mean plus or minus two standard deviations (mean ± 2sd) (Pickrell *et al.*, 1974; Kaneko, 1988; Okotie-Eboh *et al.*, 1992; Gascoyne *et al.*, 1994). Second, if the distribution is not normal, then the range may be determined by performing logarithmic transformations on the data such that a normal distribution is obtained, then applying the mean ± 2 standard deviations technique (Kaneko, 1988). Third, again for non-normal distributions, a percentile method may be adopted such that the 2.5^{th} and the 97.5^{th} percentile form the lowermost and uppermost values of the range respectively (Mbassa and Poulsen, 1993a; Mbassa and Poulsen, 1993b). However, there are a number of inherent problems associated with the reference range.

In each of these approaches approximately five per cent of the "healthy" population must be misclassified as abnormal (Slotnick and Etzell, 1990; Young, 1992). Tyler and Cullor (1989), Kidd (1991) and Romatowski (1994) have emphasised the impact that this has when a number of parameters are measured: As the number of parameters measured increases, so too does the probability of obtaining an aberrant abnormal result. Not only may this lead to confusion in the management of the unwell animal, but it is also of importance in the assessment of health screening procedures, which are increasingly popular in general practice (Gräsbeck, 1990; Gleadhill, 1994), such that healthy animals may be subjected to a form of treatment or management unnecessarily. Experienced clinicians also realise that there is a wide variation among results obtained from different cases (Edwards *et al.*, 1989). It is often the degree of deviation from the reference range which is more important than whether the value is simply within or outwith the reference range, with respect to further management of a case (Møller-Peterson, 1992; Young, 1992).

Mee (1995) highlighted a further pitfall of the reference range. An international survey was conducted in order to compare reference ranges and methodologies employed by various laboratories. For most of the biochemistry parameters which were investigated within the study, there was enormous variation with respect to the reference range adopted by the laboratory (Mee and McLaughlin, 1995). One possible explanation is that the variation of absolute biochemistry results depended upon the laboratory method adopted (Sodikoff, 1995) and thus affected the reference range established for that laboratory. However, Mee (1995) found that a proportion of the laboratories surveyed had not determined a reference range using their own instruments, but had opted for a range which had been set by an unrelated laboratory. This practice could lead to inappropriate interpretation of test results.

This study has highlighted a further problem of the reference range approach to the interpretation of clinical biochemistry. For many of the biochemistry parameters investigated, the distribution of results from a presumed healthy population data has been documented as normal (Kaneko, 1988). However, the results of the interrogation of the unwell cattle database suggested that within an unwell population of animals, the distribution of results may be skew (5.5.2). This was in keeping with findings of Gleadhill (1994) and of Little *et al.* (1994) with respect to the dog, and with respect to the horse, as described within Chapter 4. Mean and standard deviation statistics are only appropriate where the distribution of data is normal (Pickrell *et al.*, 1974; Zinkl *et al.*, 1990; Mbassa and Poulsen, 1993a), and application of such statistical methods to a population which exhibits a skew distribution may be misleading.

The reference range may therefore be of questionable value in the unwell animal. The value of ascertaining reference parameters which relate to unwell patient based populations has been recently discussed within the medical domain (Rao, 1990; Zwetsloot-Schonk, 1990; Young, 1992; Kouri *et al.*, 1994). Young (1992) noted that, "The question that a physician has of a patient is does he/she have or not have a particular disease rather than is the patient ill or well".

Given the limitations of the reference range, it is important that a more appropriate means for the interpretation of clinical biochemistry data from an unwell animal be developed.

5.6.2 Percentile analysis

Adoption of the percentile approach in this study offered a number of advantages. Percentile analysis does not assume normally distributed data and was deemed suitable for the analysis of those data from the unwell equine and cattle populations which displayed skew distributions. The percentile approach as a means for interpretation resulted in the representation of clinical biochemistry values being simplified at several levels.

First, absolute values no longer needed to be considered. For example, a urea concentration of 2.0 mmol/l in an equine case may be meaningless to those inexperienced in clinical biochemistry interpretation, or to those who, although experienced in small animal biochemistry, may be unsure of the implications in an equine case. By employing the percentile analysis technique, it may be ascertained that the value of 2.0 mmol/l lay within the bottom 1% of equine urea results from the hospital database. This meant that interpretation was facilitated because a value could be expressed simply as falling within the lowest or highest 5% or 1% of all cases previously seen, providing an immediate indication of the degree of abnormality of a result.

Second, although measures to introduce Standard International units have been in place for a number of years (Collins and Kelly, 1977), some countries, such as the United States, have been slower to adopt the convention (Kerr, 1989; Meyer *et al.*, 1992). Expression of results in percentile form negates the confusion which may arise when absolute values are expressed in different units.

Finally, the percentile method of data interpretation allowed comparison of biochemistry results which had been obtained using different biochemistry analysers. It is accepted that absolute biochemistry results vary depending on the method of analysis used and on individual instruments (Farver, 1989; Carlson, 1990; Christensen, 1992; Dart *et al.*, 1992; Mee 1995). This issue may be overcome by the expression of results in percentile form, allowing collaborative studies on a much wider scale to be conducted. In the study of the cattle population, this allowed data generated from three different biochemistry analysers to be combined, maximising the number of cases available for determination of the Biochemical Factor.

5.6.3 Bayesian approach

Bayesian analysis techniques are useful for deriving revised probabilities for states of nature given new or additional information (Ngategize *et al.*, 1986; Grieve, 1991; Fuchs *et al.*, 1993; Miettinen and Caro, 1994). Ledley and Lusted (1959) published one of the earlier papers indicating the application of Bayes' theorem (Reverend Thomas Bayes, 1702-1761) to diagnostic probabilities. The form of Bayes' theorem adopted within Chapters 4 and 5 is being used increasingly in human medicine (Henderson, 1993; Montironi *et al.*, 1996) and may be regarded simply as follows,

a posteriori odds = Likelihood Ratio • *a priori* odds

The likelihood ratio is thus a multiplication factor between the *a priori* and *a posteriori* odds (Christensen, 1992; Joseph *et al.*, 1995). Henderson (1993) suggested that, in general, a good likelihood ratio should exceed two and further indicated the possibility of calculation of confidence intervals using the χ^2 statistic.

In Chapters 4 and 5, "Biochemical Factor" was the term adopted for the likelihood ratio as it pertained to the clinical biochemistry and diagnosis data.

5.6.4 Biochemical Factor in decision support

By tabulating the diagnoses or sites which corresponded to the biochemistry results, and ranking the most frequent diagnoses or sites within each percentile band, an indication of the most likely diagnoses or sites given any biochemistry parameter result was achieved.

From Chapter 4, using the example of urea of 2.0 mmol/l which lay in the bottom 1% of all the hospital case results, the most likely diagnosis was hepatopathy. With this approach, a clinician could establish whether a biochemistry result was abnormal, the degree of abnormality, and the most likely associated diagnoses. Furthermore, the Biochemical Factor indicated how many times more likely the diagnosis was to be hepatopathy, than before the biochemistry information had been available. In this case, given that the urea value was 2.0 mmol/l, the horse was almost 16 times more likely to be diagnosed with hepatopathy than before the test result was available.

In Chapter 5, the Biochemical Factor was calculated using four different approaches - grouping of diagnoses within irregular percentile bands; grouping of diagnoses within regular percentile bands; grouping of pathological sites within irregular percentile bands; and grouping of pathological sites within regular percentile bands. The

examples of pyelonephritis and kidney within groupings for urea percentile bands were used throughout the results section for illustration of the concept. Through documented pathophysiological processes, if an animal had pyelonephritis or, more generically, a problem which involved the kidney, an increase in plasma concentration of urea would be anticipated (Finco, 1997). This association between raised urea and pyelonephritis or kidney was indeed detected using the percentile grouping and Biochemical Factor approach (5.5.5). The diagnoses and sites used for the probabilistic calculations for cattle were based on *post mortem* examinations, and were thus independent of the biochemistry result. The validity of the Biochemical Factor as a reliable means for the interpretation of clinical biochemistry results was thus substantiated.

In summary, by linking the biochemistry results with the diagnosis or pathological site data within the hospital database, the study realised the ability to quantify the relationship between biochemistry results and disease. This novel approach to clinical biochemistry data interpretation emphasised the value of further diagnostic testing and has important implications for the future of clinical biochemistry interpretation with respect to diagnostic support.

5.6.5 Biochemical Factor in parameter selection

Not only does the Biochemical Factor have potential importance in diagnostic support, it may also be applied to biochemistry parameter selection (Smith, 1991a). This may be particularly important in the general veterinary practice environment where clinicians may have to work under greater financial constraints imposed by the client.

The first consideration is the number of parameters which ought to be measured. There are two basic possibilities in this respect - a large range of parameters (for example, 15 to 20), or a smaller selection (perhaps, five to seven). There are arguments for and against each of these (Martin and Bonnett, 1987; Smith, 1991b). Measuring a large number of parameters is more expensive, and often unnecessary. It is really only of potential use when a clinician is taxed by a particular case, and is searching for any clue by which they may be guided. The biochemistry results in this situation may provide the lead required (Kerr, 1989). However, the more accepted approach to biochemical testing is to select a panel of parameters which are suspected of being helpful in the particular case. Increasingly, veterinary investigation laboratories, such as Grange Laboratories are offer organ profiles, such as liver and kidney panels (Grange Laboratories, 1997). This

method is more efficient, requires forethought by the clinician and may be more rewarding both for clinician and laboratory (Gama *et al.*, 1992).

The second consideration is identification of which parameters to select. Through increasing knowledge of pathophysiological processes, there is an awareness of many of the biochemical changes undergone in various diseases. Clinical presentation of a case may lead a clinician to suspect a particular disease, predict biochemical disturbances, and use an appropriate panel of tests to confirm or deny suspicions (Rose and Wright, 1991; Meyer *et al.*, 1992; Jensen and Høier, 1993). It is at this level that the Biochemical Factor may be of use. The higher the Biochemical Factor, the greater the potential information value in knowing the result for that biochemistry parameter, when a particular disease is suspected. By assessing the value of several biochemistry parameters using this method, an appropriate panel of perhaps five to seven parameters could be selected. This may lead to more efficient laboratory testing.

5.6.6 Study considerations

Investigating the cattle population from within the hospital database ensured the availability of *post mortem* diagnoses. These "definitive" diagnoses allowed validation of the new techniques employed to interpret the clinical biochemistry results because the diagnoses were determined independently from the clinical biochemistry results. The last plasma biochemistry panel was chosen for investigation as this was the sample taken nearest to the time of *post mortem* examination.

Importantly, the population of cattle investigated was unique to the study (Thrusfield, 1985), due to case selection bias towards cattle exhibiting disease of potential economic loss to the producer. Similarly, the equine referral hospital population, detailed in Chapter 4, is a biased population with respect to the frequency of certain diseases (Slater and Boothe, 1995). Many cases which present to general veterinary practice, may never need referral to a veterinary hospital, such as a straight forward spasmodic colic, and thus would be under-represented in a hospital population. In contrast, Cushing's disease may be over-represented. The diagnostic support is thus only directly applicable to the study hospital population. However, the percentile analysis and probability techniques may be similarly applied to any population and any species.

5.6.7 Implications of findings

Methods for the interpretation of veterinary clinical biochemistry data have not developed in tandem with the technology from which biochemistry results may be derived. As with any ancillary clinical test, the results of clinical biochemistry tests are only of value when they are appropriately interpreted (Martin and Bonnett, 1987; Shimizu *et al.*, 1990; Young, 1992). With respect to the correct application of clinical biochemistry testing, there is no substitute for a profound understanding of pathophysiological processes, and their reflection in clinical biochemistry (Loeb, 1982; Kaneko, 1988; Burke, 1995). However, recent reports have suggested that the extent to which clinical biochemistry is taught within veterinary schools and medical schools is declining (Boon and Easley, 1992; Young, 1992; Burke, 1995), and a reduced comprehension of clinical biochemistry results by new graduates may be a consequence.

Increasingly, clinical biochemistry results are generated within the practice environment (Lumsden and Jacobs, 1989; Gerrard and Little, 1994), rather than through a commercial laboratory. Although this is advantageous with respect to more immediate generation of results, 24-hour access to laboratory equipment, and better quality of sample tested (Sallee *et al.*, 1990), there is no expert interpretation of the panel of results. Thus, the requirement for comprehensible, detailed means for the interpretation of clinical biochemistry data is now essential. By employing a combination of percentile analysis and conditional probability techniques to the hospital data, the development of a means of clinical biochemistry interpretation was developed whereby a clinician could determine whether a value was abnormal, the degree of abnormality, and the most likely associated diseases. Appropriate application of the biochemistry factor techniques described offers a means for such interpretative support.

Chapters 4 and 5 have presented the data mainly from the aspect of interpretation of individual biochemistry parameters. However, often a clinician may suspect a particular diagnosis, and require to confirm or exclude that diagnosis based on a panel of biochemistry results (Christensen, 1992). In Chapter 6, disease profiles generated using the GUVS case data are presented.

CHAPTER VI

BOVINE BIOCHEMISTRY DATA ANALYSIS - PART II
DISEASE PROFILES

CHAPTER VI

BOVINE BIOCHEMISTRY DATA ANALYSIS - PART II DISEASE PROFILES

6.1 BACKGROUND

The interpretation of clinical biochemistry parameters on an individual animal level is important, as highlighted in Chapters 4 and 5. However, often the historical and clinical presentation of a case may lead a clinician to suspect a particular disease. Thus interpretation of clinical biochemistry parameters may be approached from the aspect of a disease profile. In this chapter, the Biochemical Factor results derived in Chapter 5 are used to provide a visual representation of the clinical biochemistry profile for selected diagnoses.

6.2 INTRODUCTION

In Chapter 5, techniques which may be used to aid in the interpretation of clinical biochemistry test results were described. For each biochemistry parameter under investigation, a table of the most common diagnoses for different ranges of percentile based biochemistry results was compiled (*5.5.5.1, 5.5.5.2*). For each diagnosis, a Biochemical Factor was calculated which revealed how many times more likely that diagnosis was, given the specified biochemistry result. Representation of the results based on a format reflecting individual biochemistry parameters, as illustrated in Tables 5.14 and 5.15, was important with respect to future use of the techniques for interpretation of individual biochemistry parameter results.

However, in practice, on examination of a case, a clinician builds up an image of the case which incorporates each piece of relevant information, such as historical and clinical presentation, and results of any clinical biochemistry, clinical haematology or other ancillary tests employed (Sodikoff, 1995; Eades and Bounous, 1997). The clinician then uses all the information to deduce the most likely diagnosis (Christensen, 1992), and hence the best form of management and treatment (Christensen, 1992; Cockcroft, 1995; Macartney, 1995). Often, historical and clinical presentation of a case are sufficient for

the clinician to suspect one of only a few diagnoses (Kerr, 1989; Shortliffe and Barnett, 1990; Henderson, 1993). At this stage, disease profiles of the biochemical "picture" of diseases may be of use in differentiating between different diseases. It was therefore of relevance to compile the clinical biochemistry profile for different diseases.

6.3 MATERIALS

The materials necessary for this component of the analysis were as required for Chapter 5. In brief, the last panel of biochemistry results and associated *post mortem* data pertaining to cattle seen at GUVS hospital between 1988 and 1997 were required. The data were extracted from the hospital database as described in 5.2.2. The biochemistry parameters investigated included urea, creatinine, phosphate, total protein, albumin, globulin, sodium, chloride, potassium, calcium, magnesium, alkaline phosphatase and aspartate amino-transferase. The biochemistry and *post mortem* data were in coded format according to the methods described in 5.4.1 and 5.4.2, respectively. A training set was derived as outlined in 5.3.3 by randomly selecting two-thirds of the coded dataset, and the test set consisted of the remaining third of the data. The approach of selecting two-thirds for a training set was employed by Reeves *et al.* (1990) for the development of a multivariable prognostic model for equine colic, and similar training and test set approaches have been adopted in the medical domain (Todd *et al.*, 1993).

6.4 TRAINING SET METHODS

6.4.1 Outline of probability methods

For each of the biochemistry parameters under investigation, the Biochemical Factor was calculated for each *post mortem* diagnosis within each of ten percentile band groupings. The probability techniques employed to calculate the Biochemical Factor are described in detail in 4.4.3. The Biochemical Factor represented how many times more likely a diagnosis was, given that the biochemistry result lay in a particular percentile band. It was calculated using the formula given in Equation 6-1.

$$\frac{P(B|D)}{P(B|D')}$$

Where, D represents disease, D' represents all diseases which are not disease D, and B represents percentile band B.

Equation 6-1 Formula used to calculate the "Biochemical factor" relating to each *post mortem* diagnosis, within each percentile band grouping for each biochemistry parameter under investigation.

6.4.2 Development of disease profiles

Using the Biochemical Factor results derived from employing the probability techniques, clinical biochemistry profiles were constructed for each of the five most common diagnoses. In particular, chronic suppurative pulmonary disease, endocarditis, Johne's disease, lymphosarcoma and mucosal disease were investigated. As was used for the calculation of the Biochemical Factor as described in 5.3.2, two different percentile band grouping methods were adopted, that is, irregular percentile bands and regular percentile bands, culminating in two clinical biochemistry patterns for each disease.

A table was constructed which displayed the percentile band groupings as column headings, and the 13 clinical biochemistry parameters as row headings (Figure 6-1). Each of the blank cells within the table was subsequently shaded, based on the Biochemical Factor result achieved within each percentile band grouping for each biochemistry parameter. There were four shading possibilities developed such that low Biochemical Factors were allocated light shades, progressing though to dark shades allocated to higher Biochemical Factors. Figure 6-2 indicates the shades adopted, and the associated Biochemical Factors represented.

Given that there were 10 percentile band groups and 13 biochemistry parameters, Biochemical Factor shading for a total of 130 cells was therefore required for each *post mortem* disease under investigation. For a proportion of the cells, no Biochemical Factor was calculated because the disease was never associated with a biochemistry value lying within that percentile band. These cells remained blank.

Completion of shading of the cells within the table shown in Figure 6-1 created a clinical biochemistry profile for each of the *post mortem* diagnoses investigated.

	P1 (mn - 1)	P2 (2 - 5)	P3 (6 - 10)	P4 (11 - 25)	P5 (26 - 50)	P6 (51 - 75)	P7 (76 - 90)	P8 (91 - 95)	P9 (96 - 99)	P10 (99 - mx)
Urea										
Creatinine										
Phosphate										
Total protein										
Albumin										
Globulin										
Sodium										
Chloride										
Potassium										
Calcium										
Magnesium										
AP										
AST										

Figure 6-1 Table constructed for each diagnosis under investigation. Biochemistry percentile bands (P1 to P10) are represented in column headings, while individual biochemistry parameters are represented by row headings. The percentile band grouping shown is based on irregular percentiles.

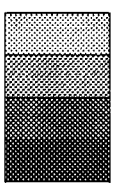


Figure 6-2 Shading template used for the representation of Biochemical Factor results calculated for each percentile band grouping for each biochemistry parameter for common *post mortem* diagnoses under investigation.

6.5 TEST SET METHODS

The test set consisted of one-third of the original dataset, as described in 6.3. This set contained cases for which a coded *post mortem* diagnosis, and associated panel of coded clinical biochemistry results was available. In order that the disease patterns developed using the methods described in 6.4 be assessed, each case with a known diagnosis was represented in a means comparable to those of the disease patterns. Thus, for each test case, a blank table identical to that displayed in Figure 6-1 was created. Thereafter, a cross was used to reflect the biochemistry result for that particular case. Because there were only thirteen biochemistry parameters, a maximum of thirteen crosses were made for each case. Figure 6-3 shows an example of the display for a test case, including only urea and creatinine for illustration.

	P1 (mn - 1)	P2 (2 - 5)	P3 (6 - 10)	P4 (11 - 25)	P5 (26 - 50)	P6 (51 - 75)	P7 (76 - 90)	P8 (91 - 95)	P9 (96 - 99)	P10 (99 - mx)
Urea				X						
Creatinine					X					

Figure 6-3 An example of part of the pattern display for a "test case", with a known *post mortem* diagnosis, with the results for urea and creatinine only included for illustration purposes. The biochemistry results are represented by "**X**". In this example, the case had a urea value which lay within P4, that is in the 11-25th percentile band; and a creatinine value which lay within P5, that is in the 26-50th percentile band.

The table for the test case was produced on a clear acetate sheet which was laid over the various disease shaded patterns developed as outlined in 6.4.2. A comparison was then drawn between the clinical biochemistry profile for the new case, and those profiles established for the different diagnoses.

Although visual comparison may have provided an indication of which disease the test case represented, it was not sufficiently robust due to the subjective nature of the assessment, as well as to the fact that only a small number of diseases had been represented using the visual patterns. The development of a numerical means for classification was therefore developed.

For each case, an index was created relating to each of the five *post mortem* diagnoses for which a pattern had been developed (6.4.2). The index was calculated by multiplying the Biochemical Factor associated with the biochemistry result achieved in

the test case for each of the biochemistry parameters. The final number based on the product of 13 Biochemical Factors was termed the "Similarity Index". Equation 6-2 details the calculation of the Similarity Index.

$$SI_{disease} = BF_{urea.Px} \times BF_{creat.Px} \times BF_{phos.Px} \times BF_{TP.Px} \times BF_{alb.Px} \times BF_{glob.Px} \times BF_{sod.Px} \times BF_{chlor.Px} \times BF_{pot.Px} \times BF_{calc.Px} \times BF_{mag.Px} \times BF_{AP.Px} \times BF_{AST.Px}$$

Where, SI was the Similarity Index for a particular disease, and BF was the Biochemical Factor associated with percentile band, P*x*, for the named biochemistry parameter.

Equation 6-2 Equation used for calculation of the Similarity Index, the product of the Biochemical Factors previously calculated using the training set, associated with the new biochemistry results achieved for each test case. The Similarity Index was calculated for each of the five *post mortem* diagnoses under investigation.

The Similarity Indices for all of the test cases were then compared to assess whether the new cases were correctly classified within each of the five disease classifications. The higher the Similarity Index for the *post mortem* disease, the more likely that classification.

6.6 RESULTS

The results are presented in two sections - the first detailing the results of the development of the clinical biochemistry profiles for the five diagnoses using the training set, and the second detailing the assessment of the disease profile patterns using the test dataset.

6.6.1 Training set

The training set consisted of 746 cattle which had biochemistry testing carried out as part of their investigation at GUVS, and which had a *post mortem* diagnosis recorded in the GUVS hospital database system. The group represented a random selection of two-thirds of cattle presented to GUVS between 1988 and 1997, meeting the criteria required for the study.

Following calculation of the Biochemical Factor for each *post mortem* diagnosis within each percentile band for each plasma biochemistry parameter, the results of which are detailed in 5.5.5, analysis focused on the five most common diagnoses, namely chronic suppurative pulmonary disease, endocarditis, Johne's disease, lymphosarcoma

and mucosal disease. For the panel of 13 clinical biochemistry parameters investigated, using the irregular percentile band grouping approach, Figure 6-4 displays the biochemistry profile pattern for Johne's disease. Figure 6-5 similarly shows the biochemistry profile for Johne's disease, but with the Biochemical Factor shading based on the regular percentile band groupings. Although the patterns differed, most notably with respect to the number of blank cells in the pattern, there was a consistency to the picture, in that, for example, dark areas of shading were apparent within the low percentiles for total protein and albumin. This indicated that the lower the albumin or total protein, the more likely the case was to have Johne's disease. Interestingly, calcium also displayed dark shades in the lower percentiles, for both the regular and irregular approaches.

Figures 6-6 and 6-7 present the clinical biochemistry profiles for mucosal disease, based on Biochemical Factors based on the irregular and regular percentile band groupings, respectively. Again, although the patterns showing the two different percentile grouping approaches differ slightly, a distinct pattern for mucosal disease is visible. Areas of dark shades, reflecting high Biochemical Factors, are evident within the high percentile bands for urea, creatinine, phosphate and albumin; whereas, for sodium, chloride and potassium, areas of dark shade appear within the lower percentile band groupings. It is also noteworthy at this stage that the biochemistry profile patterns for Johne's disease and for mucosal disease are different.

The biochemistry profiles for each of the other diagnoses investigated, lymphosarcoma, chronic suppurative pulmonary disease and endocarditis, are shown in Appendix V.

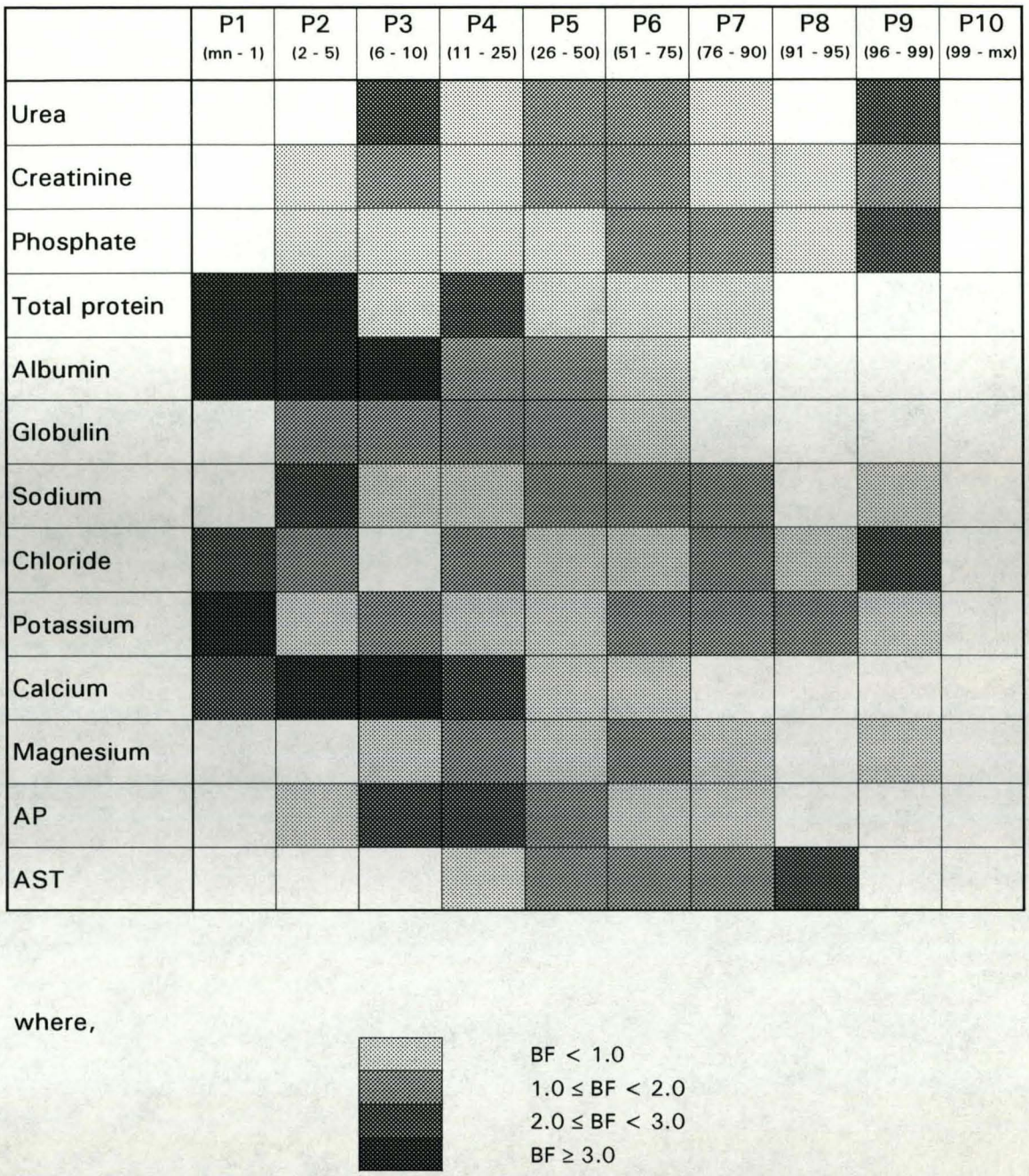


Figure 6-4 Clinical biochemistry profile for Johne's disease, based on shading from Biochemical Factors calculated using the irregular percentile grouping approach.

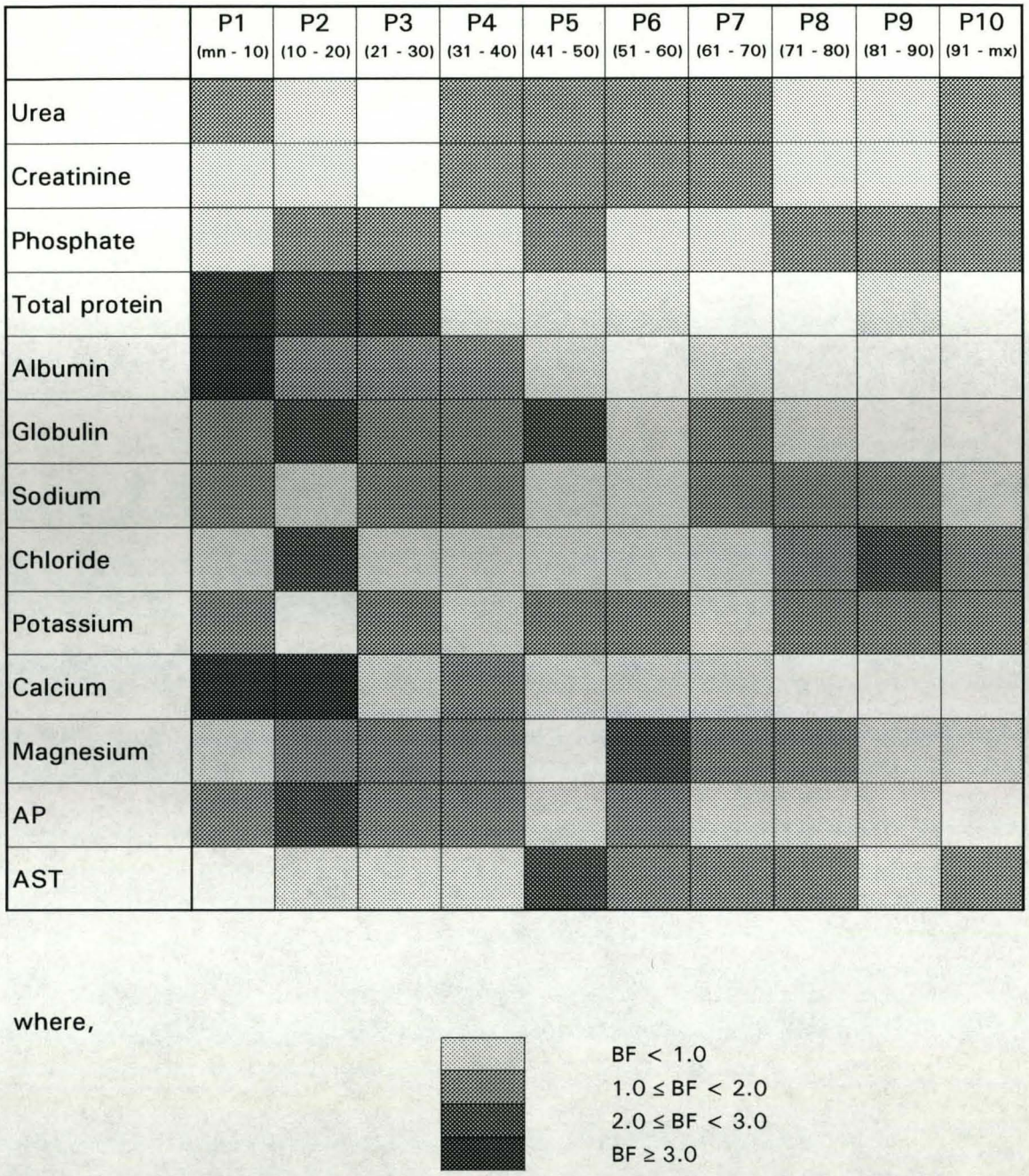


Figure 6-5 Clinical biochemistry profile for Johne's disease, based on shading from Biochemical Factors calculated using the regular percentile grouping approach.

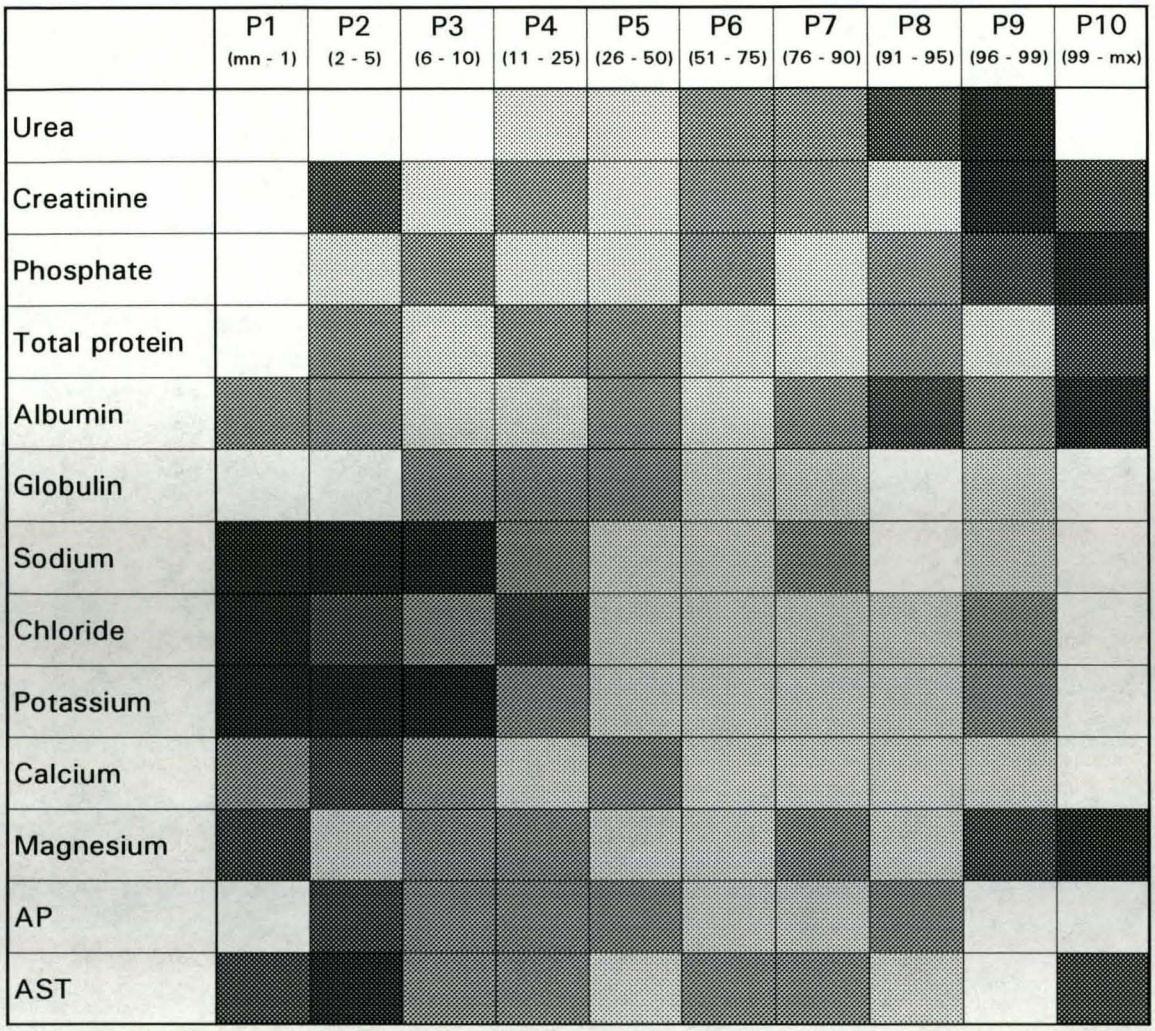
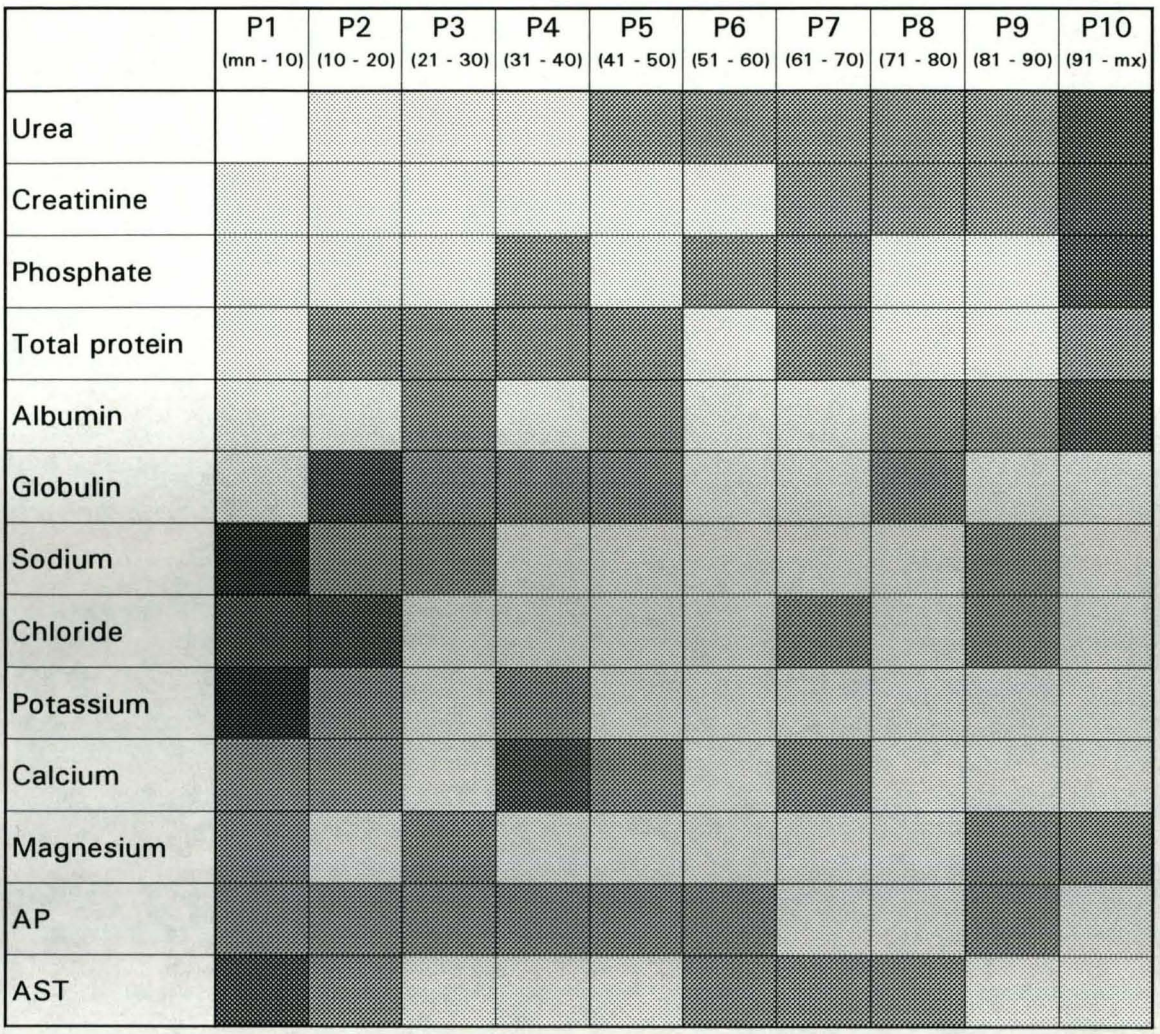


Figure 6-6 Clinical biochemistry profile for mucosal disease, based on shading from Biochemical Factors calculated using the irregular percentile grouping approach.



where,

BF < 1.0
1.0 ≤ BF < 2.0
2.0 ≤ BF < 3.0
BF ≥ 3.0

Figure 6-7 Clinical biochemistry profile for mucosal disease, based on shading from Biochemical Factors calculated using the regular percentile grouping approach.

6.6.2 Test set

6.6.2.1 Biochemistry profiles

The test dataset consisted of 350 cattle cases, each of which had a panel of biochemistry results, and associated *post mortem* examination results recorded within the GUVS hospital database system. The plasma biochemistry results and associated *post mortem* diagnoses had been coded previously as described in 5.4.1 and 5.4.2, respectively.

The five diagnoses under investigation were chronic suppurative pulmonary disease, endocarditis, Johne's disease, lymphosarcoma and mucosal disease. Table 6-1 shows the frequency of the five diagnoses within the test dataset. Mucosal disease appeared most commonly, with 30 cases in total, and lymphosarcoma appeared least commonly, with only 13 cases in total.

Diagnosis	Frequency
Mucosal disease	30
Chronic suppurative pulmonary disease	24
Endocarditis	15
Johne's disease	15
Lymphosarcoma	13

Table 6-1 Frequency within the test dataset of the five diseases for which a biochemistry disease profile pattern was developed using Biochemical Factor techniques.

For a sample of test cases, biochemistry profile patterns were constructed, where "X" marked the percentile band in which the biochemistry result lay. Figures 6-8 to 6-11 show the results for each of four cases, 121236, 122059, 123813 and 119003, laid over the appropriate disease profiles.

Figure 6-8 shows the irregular percentile band biochemistry profile for Case 121236 which had a *post mortem* diagnosis of Johne's disease. The case had a very low total protein and albumin value, lying within the lowest 5% and 1% of values, respectively. Figure 6-9 similarly shows the biochemistry profile for Case 122059, with the biochemistry results represented within regular percentile band groups. Case 122059 had low results for total protein, albumin, calcium and alkaline phosphatase, all lying within the lowest 10% of results. Case 122059 also had Johne's disease. Figures 6-10 and 6-11 show the biochemistry profiles for Cases 123813 and 119003, respectively, each of which had a diagnosis of mucosal disease. Figure 6-10 displays the biochemistry

results in irregular percentile bands, while Figure 6-11 displays the results in regular percentile bands. For both Case 123813 and 119003, high values were achieved for urea, creatinine and phosphate, yet low values were noted for sodium and chloride.

In each case, the majority of "X"s representing the biochemistry results for the case, corresponded to dark shades in the disease profile. This was indicative of a good match between the biochemistry results for the test case, and the biochemistry pattern developed using the training set.

6.6.2.2 Similarity Indices

For the 350 test cases, several Similarity Indices were calculated. For each of the five diagnoses for which a biochemistry profile pattern had been established (6.6.1), a Similarity Index was calculated using first the Biochemical Factor results based on irregular percentile bands, and second, on regular percentile bands.

Simple ranking of the 350 test cases in order of decreasing SI was expected to produce a column of diseases, such that the cases at the top with high SIs related to the disease in question. It may have been then possible to calculate a SI cut point for each disease, above which each case could be appropriately classified. However, no obvious trend was observed. For illustration, Tables 6-2 to 6-5 show twenty cases with the highest SIs for Johne's disease based on irregular percentile Biochemical Factors; Johne's disease based on regular percentile Biochemical Factors; mucosal disease based on irregular percentile Biochemical Factors; and mucosal disease based on regular percentile Biochemical Factors, respectively.

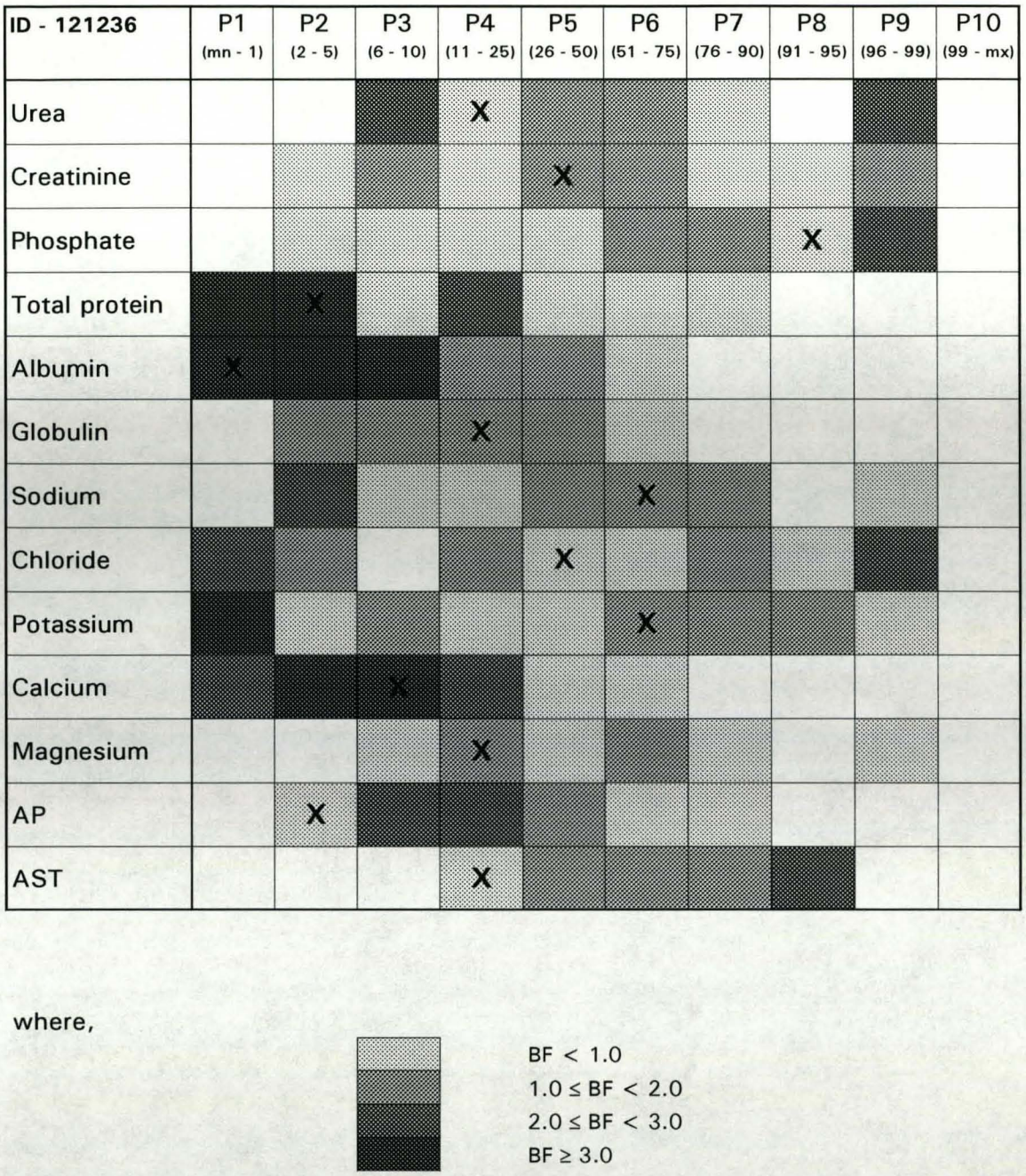


Figure 6-8 Results of the last panel of clinical biochemistry results for Case 121236, which presented to GUVS, and had a *post mortem* diagnosis of Johne's disease. The biochemistry results are classified in irregular percentile bands, and represented as an "**X**" within the appropriate cell. The profile for Case 121236 is laid over the biochemistry profile for Johne's disease. The Johne's Similarity Index was 68.1, one of the highest obtained for all 350 cattle cases assessed.

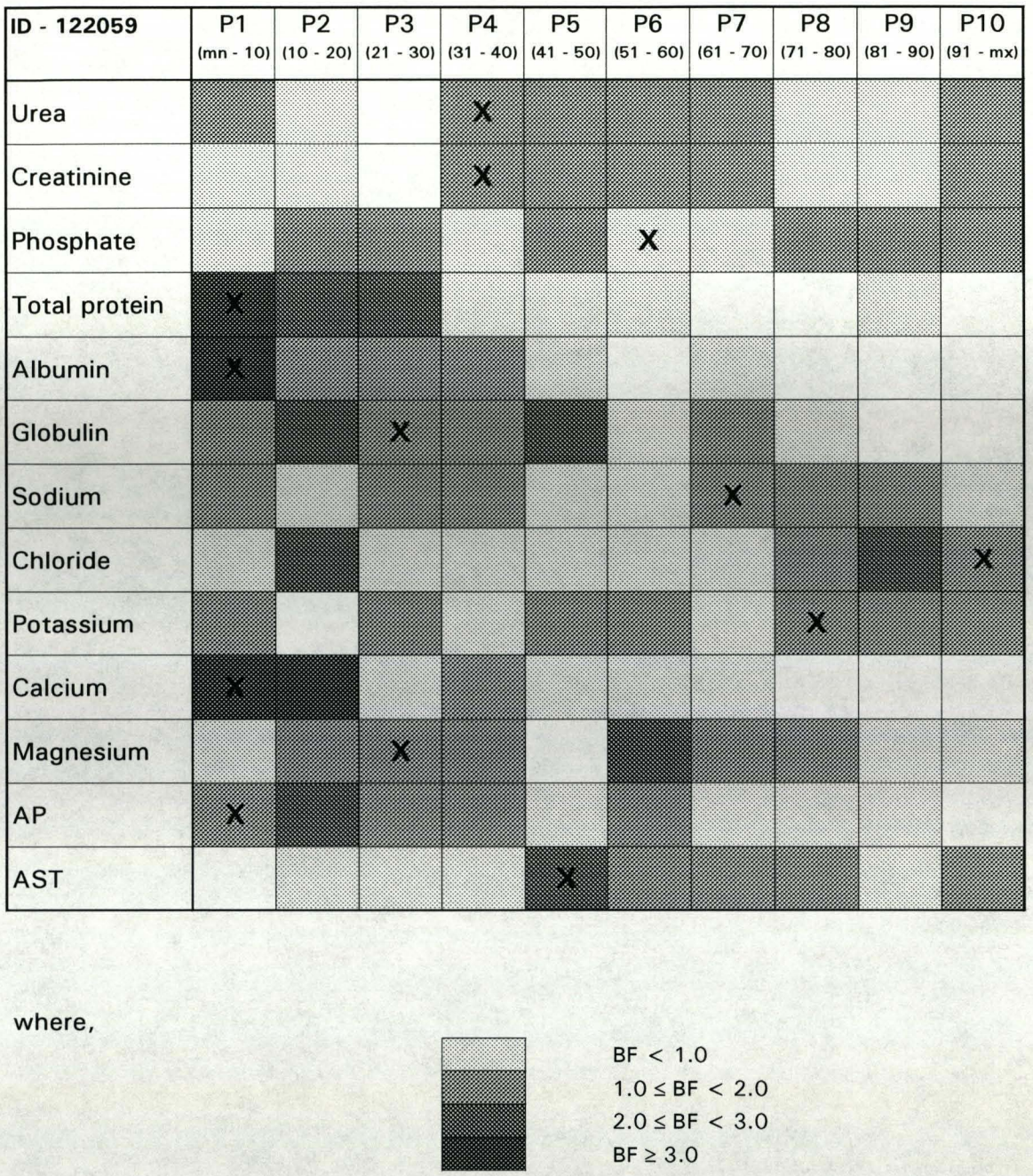


Figure 6-9 Results of the last panel of clinical biochemistry results for Case 122059, which presented to GUVS, and had a *post mortem* diagnosis of Johne's disease. The biochemistry results are classified in regular percentile bands, and represented as "**X**" within the appropriate cell. The profile for Case 122059 is laid over the biochemistry profile for Johne's disease. The Johne's Similarity Index was 1998.1, the highest obtained for all cases.

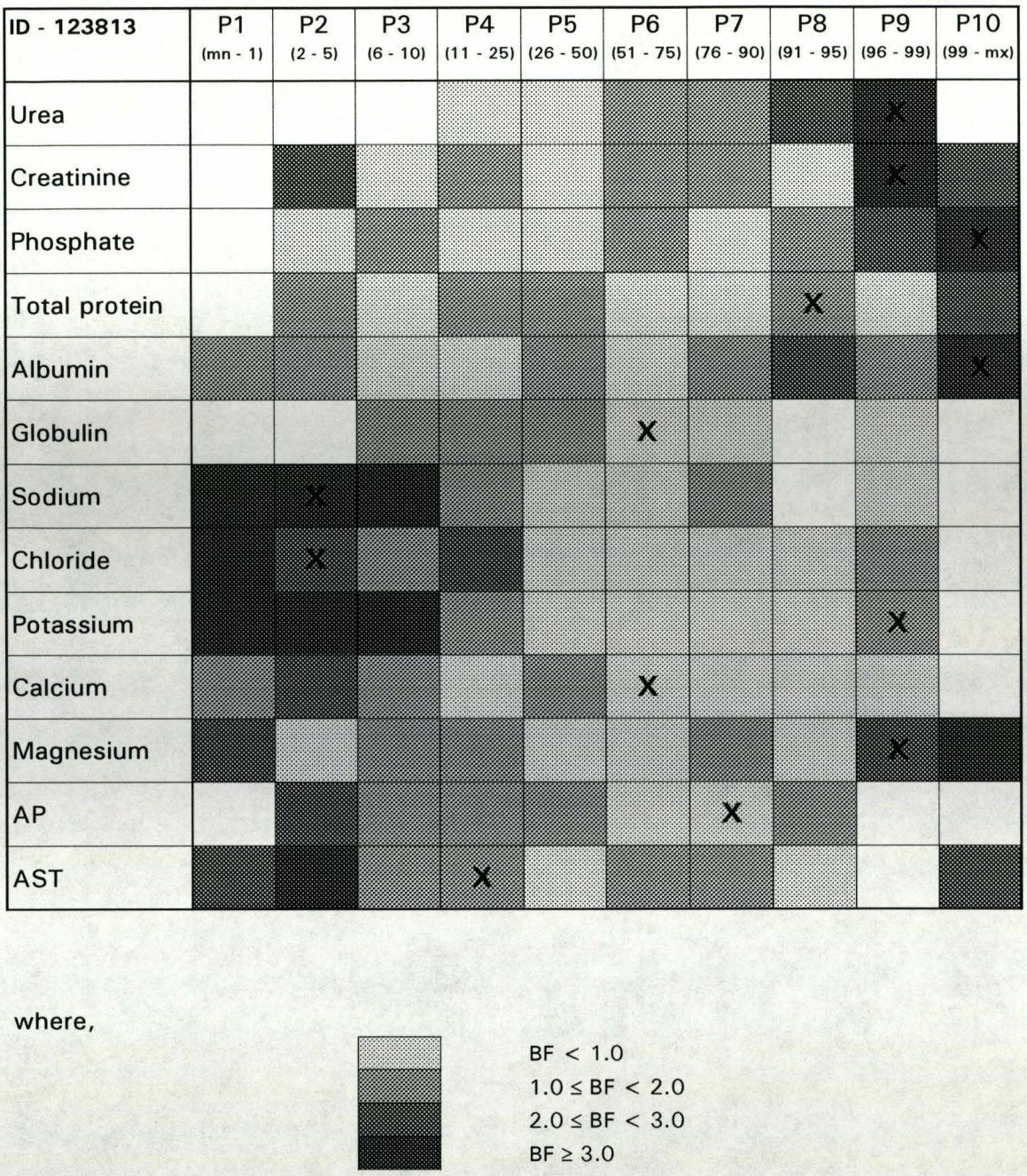


Figure 6-10 Results of the last panel of clinical biochemistry results for Case 123813, which presented to GUVS, and had a *post mortem* diagnosis of mucosal disease. The biochemistry results are classified in irregular percentile bands, and are represented by an "**X**" within the appropriate cell. The profile for Case 128813 is laid over the biochemistry profile for mucosal disease. The Mucosal Similarity Index was 11453.1, one of the highest obtained for all cases.

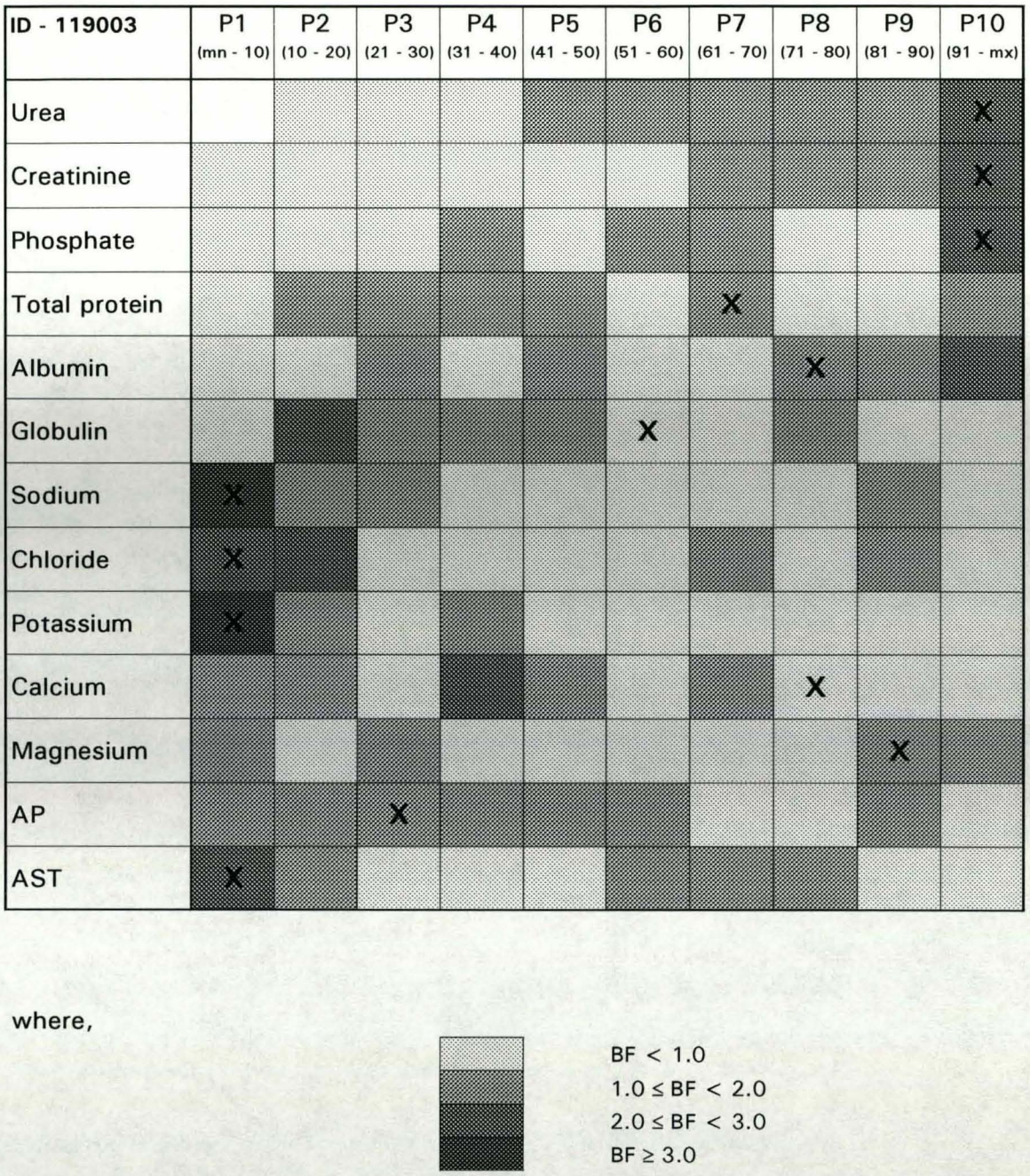


Figure 6-11 Results of the last panel of clinical biochemistry results for Case 119003, which presented to GUVS, and had a *post mortem* diagnosis of mucosal disease. The biochemistry results are classified in regular percentile bands, and are represented by an "**X**" within the appropriate cell. The profile for Case 119003 is laid over the biochemistry profile for mucosal disease. The Mucosal Similarity Index was 327.3, one of the highest obtained for all cases.

Hosp No.	Diag. code	*Post mortem* diagnosis	SI*
129884	52	Ostertagiasis	569.8
129849	54	Traumatic pericarditis	370.4
110344		Enzootic haematuria	161.4
125471	37	Johne's disease	90.9
121236	37	Johne's disease	68.1
115634	63	Renal amyloidosis	57.3
118660	22	CSPD†	37.3
128993	22	CSPD	31.9
124375	70	Abomasal ulceration	21.7
132225	37	Johne's disease	20.7
124672	52	Ostertagiasis	15.8
123812	54	Traumatic pericarditis	14.3
109937	7	Bloat	14.3
131847		Inconclusive	11.7
113534	55	Peritonitis	9.7
128130	41	Malignant catarrhal fever	9.0
132277	37	Johne's disease	7.4
109606	22	CSPD	5.6
116390	44	Mucosal disease	4.8
129480	30	Enteropathy	3.6

*Similarity Index; †Chronic suppurative pulmonary disease

Table 6-2 Test cases with the twenty highest Similarity Indices for Johne's disease, based Biochemical Factors calculated within irregular percentile band groups.

Hosp No.	Diag. code	*Post mortem* diagnosis	SI*
122059	37	Johne's disease	1998.1
120877	63	Renal amyloidosis	1066.7
111571	29	Enteritis	300.0
128130	41	Malignant catarrhal fever	257.5
121236	37	Johne's disease	150.0
109218	54	Traumatic pericarditis	68.2
129849	54	Traumatic pericarditis	52.1
125471	37	Johne's disease	49.9
115634	63	Renal amyloidosis	37.8
109606	22	CSPD†	31.1
132277	37	Johne's disease	22.6
115353		Hernia-inguinal	22.2
109937	7	Bloat	16.4
112272	55	Peritonitis	6.1
108899	29	Enteritis	5.7
128993	22	CSPD	4.3
124375	70	Abomasal ulceration	3.0
131925	11	Cardiomyopathy	2.6
112086	59	Pneumonia-chronic	2.0
127777	40	Lymphosacroma	1.9

*Similarity Index; †Chronic suppurative pulmonary disease

Table 6-3 Test cases with the twenty highest Similarity Indices for Johne's disease, based on Biochemical Factors calculated within regular percentile band groups.

Hosp No.	Diag. code	*Post mortem* diagnosis	SI*
123813	44	Mucosal disease	11453.1
110354	29	Enteritis	2392.4
114508	44	Mucosal disease	1456.5
116381	40	Lymphosacroma	779.0
118719	37	Johne's disease	413.0
114112	58	Pneumonia	205.4
111285	22	CSPD†	201.1
121905	44	Mucosal disease	125.0
119003	44	Mucosal disease	62.8
120989	37	Johne's disease	55.2
120699	44	Mucosal disease	53.1
128003	11	Cardiomyopathy	52.4
111172	44	Mucosal disease	46.9
118658		Intussusception	43.6
131388	59	Pneumonia-chronic	38.8
116474	61	Pyelonephritis	35.3
127875	37	Johne's disease	34.5
126686	30	Enteropathy-chronic	27.8
129873	44	Mucosal disease	27.4
124572	19	Congenital cardiac defect	21.1

*Similarity Index; †Chronic suppurative pulmonary disease

Table 6-4 Test cases with the twenty highest Similarity Indices for mucosal disease, based on Biochemical Factors calculated within irregular percentile band groups.

Hosp No.	Diag. code	*Post mortem* diagnosis	SI*
119003	44	Mucosal disease	627.3
120877	63	Renal amyloidosis	547.3
129917	44	Mucosal disease	340.3
114508	44	Mucosal disease	285.8
112602	37	Johne's disease	205.6
110354	29	Enteritis-non specific	192.9
120989	37	Johne's disease	166.3
128003	11	Cardiomyopathy	159.3
111285	22	CSPD†	128.9
114112	58	Pneumonia	114.3
123402	44	Mucosal disease	61.2
111172	44	Mucosal disease	61.1
116381	40	Lymphosacroma	46.3
127875	37	Johne's disease	40.9
118719	37	Johne's disease	34.2
131388	59	Pneumonia-chronic	32.1
123813	44	Mucosal disease	28.1
120699	44	Mucosal disease	23.6
118552	11	Cardiomyopathy	17.8
129873	44	Mucosal disease	16.3

*Similarity Index; †Chronic suppurative pulmonary disease

Table 6-5 Test cases with the twenty highest Similarity Indices for mucosal disease, based on Biochemical Factors calculated within regular percentile band groups.

Although in each case, some of the cases were correctly associated with the top ten SIs, only in the case of the SIs calculated for mucosal disease, based on Biochemical Factors derived using regular percentile groupings (Table 6-5), was there an indication that the high SIs related to mucosal disease.

6.7 DISCUSSION

Clinical biochemistry plays an increasingly important part in the investigation of many cases with which the busy practising clinician is faced (Feldman and Thomason, 1989; Boon and Ealsey, 1992; Magid, 1992). The requirement for access to quick and reliable means for the interpretation of clinical biochemistry parameters is therefore at a premium. As detailed in Chapters 4 and 5, with respect to horses and cattle, respectively, the current guide to interpretation, based on a reference range, has many limitations when dealing with an unwell population. Furthermore, a combined percentile and probabilistic approach which countered some of the problems the reference range poses was described. The reference range indicates the parameter results which may be expected within a "healthy" animal. Conversely, it may be of equal importance to consider the parameter results which may be expected in an unwell animal suffering from a particular disease condition. The approach described throughout Chapters 4 and 5 has thus been expanded to provide clinical biochemistry interpretation from the position of the suspected disease, rather than from the position of raw biochemistry data.

The combination of the percentile and Biochemical Factor approach, presented in the visual format described in this chapter is original. However, recent publications in small animal and equine press suggest that visual representation of clinical data may become increasingly common. Sodikoff (1995) presents a large number of small animal disease conditions in terms of disease profiles, detailing not only clinical biochemistry, but also haematology and urinalysis, in a simple visual format. The clinical biochemistry picture indicates simply whether a parameter value would be expected to be raised, normal, or lowered, with a different shade of grey to reflect each classification. Developed using expert opinion, rather than hard data, and based on a reference range approach, there may be associated shortcomings. However, it creates a simple, clear biochemistry profile for each disease, and is well presented. Similar disease profiles have been recently published in the equine press by Eades and Bounous (1997). In human medicine, means of representing data in a clear visual manner have also been sought

(Hoeke *et al.*, 1991; Niwa *et al.*, 1991), emphasising the importance for all clinicians to embrace graphical methods for clinical biochemistry interpretation.

The visual patterns of biochemistry results presented for a selection of diseases as described in this chapter may provide a platform from which interpretation in the veterinary domain may move forward in this regard.

6.7.1 Biochemistry profiles

By making use of data from a maximum of 746 cattle case which were referred to the University of Glasgow Veterinary School, biochemistry profiles pertaining to five different diseases were developed. In particular, mucosal disease, chronic suppurative pulmonary disease, endocarditis, Johne's disease and lymphosarcoma were investigated. For each disease, a visual representation of the biochemistry profile based on Biochemical Factors was created. A total of thirteen biochemistry parameters were included within the picture, and for each of ten percentile band intervals a coloured shade indicated how many times more likely the disease was, given a biochemistry result within that percentile band.

The biochemistry patterns were developed using two approaches - the first based on Biochemical Factors calculated using irregular percentile groupings and the second based on Biochemical Factors calculated using regular percentile groupings. As anticipated, the pattern generated for each diagnosis was similar for each of the two approaches. The regular percentile approach was adopted because it allowed calculation of Biochemical Factors within percentile bands to be based on approximately equal numbers, and, therefore, negated any influence of sample size on the results. However, it was concluded that, given the similarity of the profiles for the two approaches, the irregular percentile approach was preferable due to the fact that it highlighted areas of presumed clinical importance, that is, biochemistry parameter concentrations within the top one, five or ten per cent. Such percentiles may be used as important benchmarks by clinicians coming to a diagnosis.

However, comparison of the patterns among the five diseases investigated indicated differences. The results for Johne's disease and mucosal disease were highlighted within the results section for illustration. The Johne's disease pattern most notably showed areas of dark shading within the low percentiles for total protein, albumin and calcium, reflecting high Biochemical Factors for Johne's disease in

association with the low biochemistry results. This suggested that, given very low plasma total protein, albumin or calcium results, Johne's disease was more likely than before the biochemistry information was known. This was not only of statistical importance, but also was logical from a clinical point of view. Johne's disease is a cattle illness caused by *Mycobacterium paratuberculosis* (Blood and Radostits, 1989b). It is a disease most commonly seen in cattle aged 3 to 5 years and is associated with chronic diarrhoea and weight loss. The organism localises in the mucosa of the small intestine and causes a thickening of the intestinal wall resulting in a protein losing enteropathy (Blood and Radostits, 1989b; Hornbuckle and Tennant, 1997). The clinical pathological profile, based on knowledge of the pathophysiological processes, includes low plasma albumin, and consequently low plasma total protein. Plasma calcium is albumin bound, therefore, low plasma albumin is associated with an artificially low plasma calcium (Rosol and Capen, 1997). This brief outline of the salient features of Johne's disease confirms the value and validity of development of a clinical biochemistry profile based on actual cases.

The pattern for mucosal disease highlighted areas of dark shades, reflecting high Biochemical Factors, within the high percentile bands for urea, creatinine, phosphate and albumin; whereas, for sodium, chloride and potassium, areas of dark shade appear within the lower percentile band groupings. Mucosal disease was one of the most common diseases affecting the cattle presenting to GUVS. It occurs in animals persistently infected with the BVD-MD (Bovine Virus Diahrroea-Mucosal Disease) virus (Blood and Radostits, 1989a). Clinical signs range from diarrhoea, to mouth ulcers, interdigital ulceration, lameness and skin lesions - a multi-systemic condition. Mucosal disease is most often seen in cattle between the ages of six months to two years of age, and diagnosis is usually made on the basis of characteristic clinical or pathological lesions. Due to the multi-systemic nature of mucosal disease, the clinical pathology profile associated with mucosal disease may be variable. It would be interesting to investigate the pattern derived using the GUVS cases in more detail in a future study.

6.7.2 Biochemistry profile verification

Although the findings of the differing biochemistry profiles for each disease were encouraging, it was important that the data profile techniques be independently assessed (Christensen, 1992). Following completion of the biochemistry profiles for each disease, a total of 350 test cases, with a set of biochemistry results and *post mortem* diagnosis

recorded within the GUVS hospital database, were used to ascertain whether the biochemistry profiles for each disease could be employed to accurately classify cases into appropriate disease groups.

For a number of the test cases, an individual biochemistry profile comparable with that created for the disease profiles was compiled. The case pattern was overlaid on each of the disease patterns generated, and the agreement of the two patterns was assessed. There was large variation in the correlation of the cases with known disease with that of the disease profile, with some cases matching closely the disease pattern, and others less so. In order that the agreement be assessed more objectively, a Similarity Index was calculated for each of the 350 test cases. The SI was a product of the Biochemical Factors associated with each parameter result achieved for the test case. The results of the SI calculations suggested that the SI could not be used for accurate classification of cases, at least for the five diseases investigated. The reasons for this may be several fold - the small number of cases of each disease in the study; the influence of concurrent disease; the assumption of independence; selection of too many biochemistry parameters; and reliance on the biochemistry profile alone for a diagnosis.

First, although the cattle database maintained at GUVS was large, containing over 1000 cases with details of biochemistry test results and *post mortem* diagnosis, the number of cases within individual disease groups was much less. For example, the disease pattern for mucosal disease, the most common diagnosis, was based on only 57 cases. In fact, mucosal disease yielded the most encouraging results with respect to accurate classification, as displayed in Table 6-5, where most of the cases with high similarity indices for mucosal disease, calculated based on regular percentile bands, actually were cases of mucosal disease. The numbers of cases available in the cattle database for each disease may be compared, for example, to those used by Reeves *et al.* (1990) in the development of a colic model based on a total of 1965 equine colic cases. Thus, the poor performance of the disease profile and Similarity Index may be a function of low numbers.

Second, it must be appreciated that this is a unique population with respect to the cattle under consideration, and that due to the nature of the referral cases which present to GUVS, outlined in 5.2.1, the cattle may suffer from concurrent disease. Although the diagnosis used for statistical analysis throughout Chapters 5 and 6 was the primary

diagnosis only, it is possible that a secondary disease may have contributed to any biochemical abnormality.

Multiplication of the Biochemical Factors associated with the biochemistry results for a given case assumed independence of the biochemistry parameters. This assumption may not be entirely valid (Kerr, 1989; Dart *et al.*, 1992; Jacobs *et al.*, 1992), and inaccurate results may have been generated. Therefore, the case assessment procedure may not have been reliable. Overcoming this problem would require complex mathematical formulae, taking into consideration quantitative parameter dependence. Development of such an equation may be a future possibility, but it would demand a much greater data resource than was available from the GUVS cattle database alone, for example, thousands of cases of each disease, with complete biochemistry data listings.

Also, the greater the number of biochemistry parameters within the pattern profile, in this case a total of thirteen, the greater the number of cases required to statistically substantiate a pattern. A simple rule dictates that 2^r cases are required, where r is the number of variables under consideration. Thirteen variables would therefore require at least 8192 cases of each disease, far in excess of that available in the GUVS cattle database. This problem may be surmounted by the selection of a few parameters designated as key for each disease. Not only would this aid in the demand for the number of cases required, as detailed in 5.6.5, it is the more desirable approach to clinical pathology, termed the "panel approach" by Sodikoff (1995).

Finally, rarely is a clinical pathological profile pathognomic for a disease (Martin and Bonnett, 1987; Young, 1992). As detailed within Chapter 4, most diagnoses are made using all the information available to the clinician: historical, clinical, haematological, biochemical, pathological, and so on, rather than relying on any one parameter result (Martin and Bonnett, 1987; Cote and Hoff, 1991; Smith, 1991b; Young, 1992; Gräsbeck, 1990). Clinical biochemistry tests often provide contributory diagnostic evidence, but do not necessarily offer a diagnostic decision (Henderson, 1993; Joseph *et al.*, 1995). Therefore, assertion of a diagnosis based on a panel of clinical biochemistry results alone was an optimistic goal for this aspect of the study.

6.7.3 Future considerations

The biochemistry profiles and test case classification centred on the ability of the patterns to classify, for example, a case as having mucosal disease, or as *not* having mucosal

disease. Another approach could be the differentiation between two diseases. A Biochemical Factor could be similarly calculated in this respect. In Chapter 4, the odds in favour of an event B given event A was expressed as shown again in Equation 6-3.

$$\frac{P(B|A)}{P(B'|A)} = \frac{P(A|B).P(B)}{P(A|B').P(B')}$$

Equation 6-3 The odds in favour of event B occurring compared to event B not occurring, given that event A has already occurred.

An expression detailing the odds in favour of event B_1 compared to event B_2, could be similarly derived (Equation 6-4).

$$\frac{P(B_1|A)}{P(B_2|A)} = \frac{P(A|B_1).P(B_1)}{P(A|B_2).P(B_2)}$$

Equation 6-4 The odds in favour of event B_1 occurring compared to event B_2 occurring, given that event A has already occurred.

This form of the equation could be applied to the particular situation regarding diagnosis and biochemistry results, as shown in Equation 6-5.

$$\frac{Pr(D_1|B)}{Pr(D_2|B)} = \frac{Pr(B|D_1).Pr(D_1)}{Pr(B|D_2).Pr(D_2)}$$

Equation 6-5 Equation which represents the odds in favour of diagnosis D_1 compared to diagnosis D_2, given a biochemistry parameter value in percentile band B.

This form of the equation would enable, for example, calculation of the Biochemical Factor, $Pr(B|D_1)/Pr(B|D_2)$, for mucosal disease compared to Johne's disease, given a particular biochemistry parameter concentration. This could allow the implementation of the pattern technique at the bottom of a decision tree incorporating signalment, historical and clinical information. This potential use of Bayes equation has received little attention for decision support, despite it being the subject of a mathematical investigation by Laplace in 1774 (Stigler, 1986).

Although the disease pattern profiles and Similarity Indices could not be used to classify accurately new cases into appropriate disease groups, it would be interesting to investigate the clinical biochemistry pattern associated with different pathological sites.

These would be associated with greater case numbers and this alone would enhance reliability of any results. Also, pathophysiological disturbances associated with sites, such as liver or kidney, may be more readily established compared to those associated with individual diseases.

6.8 CONCLUSION

Although statistically the pattern matching approach to the investigation of the clinical biochemistry profile of different *post mortem* diagnoses did not provide a reliable means for the interpretation of biochemistry profiles, examination of the different patterns derived for each of the diagnoses investigated suggested that the patterns were clinically sensible. If more data were available, then more complex patterns could be developed which could take into consideration parameter dependence. If refinement of the techniques described was feasible, a new visually appealing approach to the interpretation of biochemistry parameter profiles may be derived.

The multi-dimensional nature of the data, that is, the large number of outcome diagnoses and large number of potential explanatory variables, coupled with the small number of cases available for individual diseases presented difficulties for multivariable analysis. One possible means of improving the performance of the data is to reduce the number of possible outcomes. Chapter 7 discusses the ability of laboratory parameters to differentiate simply between cattle with acute and chronic inflammatory processes.

CHAPTER VII

APPLICATION OF LOGISTIC REGRESSION TO CLINICAL LABORATORY INDICES TO DIFFERENTIATE BETWEEN ACUTE AND CHRONIC INFLAMMATION IN CATTLE

CHAPTER VII

APPLICATION OF LOGISTIC REGRESSION TO CLINICAL LABORATORY INDICES TO DIFFERENTIATE BETWEEN ACUTE AND CHRONIC INFLAMMATION IN CATTLE

7.1 BACKGROUND

Throughout this thesis, information which could be realised from interrogating clinical biochemistry data from the University of Glasgow Veterinary School has been investigated. By associating clinical biochemistry results with corresponding diagnosis data, quantitative links between clinical biochemistry results and diagnoses have been established (Chapters 4, 5, 6). However, one of the problems which was encountered, with respect to which statistical methods may be suitably employed, was the large number of possible outcomes, i.e., diagnoses. Seeking to identify a pattern of clinical biochemistry results for individual diagnoses proved difficult due to the small number of cases with the same diagnosis. This was particularly evident because the population under investigation was referral and displayed a high proportion of rare conditions. In Chapter 5, this diversity of outcomes was addressed in part by grouping diagnoses into relevant organ systems.

This chapter focuses on data from a study investigating the use of clinical laboratory parameters to differentiate between cattle with acute and chronic inflammatory processes. The response variable consisted of only two groups, acute and chronic, and this smaller dataset was suitable for investigation using multiple logistic regression techniques.

7.2 INTRODUCTION

Consumer confidence in food products is of enormous importance to the meat industry (Butler, 1996a; Butler, 1997b; Collee and Bradley, 1997a; Veterinary Record, 1997e). There have been several instances recently where loss of consumer confidence, often disproportionate to estimated risks, has required careful political management in an

attempt to minimise long term damage to the industry. In particular, the identification of a new variant of Creutzfeldt-Jacob disease (nvCJD) (Davies *et al.*, 1993; Sawcer *et al.*, 1993), analogous to Bovine Spongiform Encephalopathy (BSE), has caused widespread public alarm (WHO Memorandum, 1993; Smith and Cousens, 1996; Lee and Harrington, 1997; Veterinary Record, 1997c). Although there is to date no scientific proof of causality between ingestion of BSE infected meat and nvCJD (Will, 1997; Collee and Bradley, 1997b), such links are hypothesised (Almond *et al.*, 1995; Bruce *et al.*, 1997; Hill *et al.*, 1997; Lasmézas *et al.*, 1996; Portegies and Enting, 1996), and media reports have led to consumer distrust of the British meat industry (Bennett and Hallman, 1998; Butler, 1997a; Veterinary Record, 1997d). In Scotland, the more recent outbreak of food poisoning caused by *Escherichia coli* O157, which affected over 500 people, and resulted in over 18 deaths, further weakened the position of the UK meat industry (Butler, 1996b; Smyth and Connor, 1997; Veterinary Record, 1997b). The general public has, as a result, become increasingly aware of apparent inadequacies within the British meat industry (Veterinary Record, 1997a), and this has led to open questioning of meat preparation and inspection processes (Butler, 1996a).

7.2.1 Current Meat Inspection Processes

The standard of meat production and inspection in the United Kingdom has in the past been regarded as the highest not only in the European Community (Johnston, 1993), but in the world (Ryder, 1990). For many years the basic format for meat inspection has been based on an *ante mortem* inspection carried out within 12 hours prior to slaughter, followed by a *post mortem* inspection. *Ante mortem* inspection allows separation of animals which are obviously abnormal from those which are deemed normal (Gracey and Collins, 1992). Those cattle suffering from particular conditions may be identified, immediately condemned, and therefore prevented from entering the food chain. Animals suffering from lesser, localised conditions, such as lameness, may also be identified at *ante mortem* inspection, and tagged such that carcass and organs can be followed through the slaughter line, and judged as appropriate at *post mortem* inspection. Gracey and Collins (1992) stated that efficient *ante mortem* inspection can reduce *post mortem* carcass condemnation by 50%. *Post mortem* inspection allows detection and elimination of abnormalities, including contamination, ensuring that only meat fit for human consumption is passed for food.

Of particular concern is the ability to detect diseased animals prior to entering the food chain. Such animals may be carrying pathogens of zoonotic significance or pathogens adversely affecting product quality (Franco, 1988; Gracey and Collins, 1992). Currently, the approach to meat inspection is largely subjective (Saini and Webert, 1991), and the recent public scares have highlighted inadequacies of this system. There are several groups of researchers examining the possibility of objective, practical animal-side tests which may be carried out immediately prior to slaughter to identify those animals whose meat may pose a risk to the consumer (Saini and Webert, 1991; Sheffield *et al.*, 1994; Francisco *et al.*, 1996).

7.2.2 Clinical care of cattle in the field

The cow is a production animal, and as such its veterinary care must be conducted in an appropriate manner. There are two key features which distinguish medical care pertaining to cattle from that of companion animals - cattle will ultimately be used to provide food for humans; and the farmer, under whose care the cattle exist, is running a business (Fetrow *et al.*, 1985). These factors are important with respect to how the cattle should be treated, which antibiotics may be safely administered with appropriate attention to meat and milk withdrawal times, as well as to whether to treat or not. Cattle health may be managed on a herd level (Smith, 1991a; Thrusfield, 1995), rather than directed towards an individual animal. Despite farmers' vigilance, without the development of health schemes to screen cattle herds, the number of cattle suffering from clinical illnesses may increase. Such animals may not only be of poor productive capacity, but ultimately their meat may be of poor quality or even unsafe to the consumer.

7.2.3 Objectives of GUVS based study

A large number of cattle cases are referred to the University of Glasgow Veterinary School Hospital each year (Chapters 3, 5). The cattle investigated present with a variety of conditions at different stages from acute to chronic. Gracey and Collins (1992) stated that an animal with acute inflammatory processes was potentially more dangerous to the consumer than an animal with chronic inflammatory processes. The GUVS cattle population provided an ideal resource from which an investigation of the use of clinical laboratory parameters for differentiating between animals with acute and chronic inflammatory processes could be undertaken.

7.3 MATERIALS AND METHODS

7.3.1 GUVS cattle referral cases

Eighty-one cattle cases which presented to the GUVS were included in the study. The presence of inflammation was ascertained by one experienced cattle clinician based on an evaluation of the duration of illness, demeanour, clinical findings, and lesions characteristic of a likely specific diagnosis. For example, a calf with congenital cerebellar hypoplasia was classified as a non-inflammatory condition for the purposes of this work. The clinician then assigned the cattle to one of two groups designated as having either acute or chronic inflammatory processes. This was done without knowledge of laboratory parameter results.

The details of the classification system and the breakdown of the diagnoses for the clinical cases have been described previously (Horadagoda *et al.*, 1994), but were, briefly, as follows. The designation was based on the speed of onset and duration of illness, change in body condition, demeanour, rectal temperature, presence or absence of pain, and the clinical findings specific to individual organs or systems irrespective of whether a precise or probable diagnosis was made. The presence of acute inflammation was judged by the following features: sudden onset clinical signs usually with fever and dullness, and the presence of clinical signs indicative of acute inflammation in a particular organ or system, such as hot, painful joint swellings or auscultatory findings consistent with acute pneumonia. In some cases of acute inflammation, the state was an acute exacerbation of a pre-existing chronic disease state, for example an acute pneumonia, and the clinician's judgement was used to assess the various presenting features. Chronic inflammation was judged present when the disease was of longer duration, often with accompanying weight loss, the absence of fever, and, except in certain conditions such as reticular adhesions, an absence of pain. In some conditions where a precise specific diagnosis could be made at the time of presentation, for example malignant catarrhal fever, the assessment of the type of inflammation was made on the clinician's knowledge of the features of the disease, which in the case of malignant catarrhal fever was acute inflammation. In diseases where there was a clinical diagnosis at the time of first presentation which could include both acute and chronic inflammation, for example, traumatic reticulo-pericarditis, the designation as either acute or chronic inflammation was based on the clinical presentation such that an acute case was an animal with clinical

evidence of an early lesion and a chronic case had evidence of an advanced lesion, usually the presence of congestive heart failure. All the cattle examined clinically for this study received a *post mortem* examination at varying times after the initial presentation. In all cases, the post mortem findings confirmed assessment of the presence of inflammation and its classification as either acute or chronic.

Thirty-one cases were classified as having acute inflammatory processes, and 50 were classified as having chronic inflammatory processes. For each case, a total of 29 clinical laboratory parameters were obtained. These included routine clinical biochemistry parameters - urea, creatinine, phosphate, sodium, potassium, albumin, globulin, total protein, glutamate dehydrogenase (GLDH), magnesium, chloride, calcium, alkaline phosphatase (AP), gamma-glutamyl transferase (GGT), bilirubin and aspartate amino-transferase (AST); haematology parameters - white blood cells (WBC), red blood cells (RBC), polymorphonuclear cells (PMN), basophils (BASO), band polymorpho-nuclear cells (BPMN), eosinophils (ESO), monocytes (MONO), lymphocytes (LYM), packed cell volume (PCV) and haemoglobin concentration (Hb); and acute phase protein parameters - serum amyloid-A (SAA), haptoglobin (HP) and α_1-acid glycoprotein (AGP).

7.3.2 Data manipulation and statistical methods

The clinical laboratory data were imported into an Excel workbook, with details of case and sample identification, and signalment information. The cases were divided into acute and chronic groups as appropriate, and coded zero for chronic cases and one for acute cases. The coded data were then exported to a Minitab worksheet, where initial analysis was performed. First, outliers were identified and validated by referral to hard copy. Subsequently, basic descriptive statistics were obtained for each of the 29 laboratory parameters within the acute and chronic groups. Univariable analysis was performed using Student's two-sample t-tests to ascertain which parameters demonstrated a significant difference between acute and chronic groups. All those variables significant at $P<0.1$ were then included in the multivariable analysis. Stepwise logistic regression was performed using the statistical software package, BMDP (BMDP Statistical Software, Inc.). The specific form of the logistic regression model was as follows:

$$P = \frac{e^{\beta_0+\beta_1 x_1+\ldots+\beta_k x_k}}{1+e^{\beta_0+\beta_1 x_1+\ldots+\beta_k x_k}}$$

With the logit transformation, g, defined as

$$g = \ln[P/1-P]$$
$$= \beta_0 + \beta_1 x_1 + \ldots + \beta_k x_k$$

where P is the probability (of acute inflammation), β_i are model coefficients, and x_i are the explanatory variables.

Three multivariable logistic regression models were developed. The first model was developed using only the routine clinical biochemistry parameters. The second multivariable model was developed using the clinical biochemistry and haematology parameters. The third was developed using these routine parameters, plus the three acute phase protein parameters. Parameters were retained in the multivariable model at $P<0.1$. The model parameters were then entered to the statistical software package, Statistix (Sx) (Analytical Software), which facilitated further assessment of the model. Finally, the sensitivity and specificity of the three multivariable models were calculated for a range of predicted probability cut points (Reeves *et al.*, 1990; Reeves *et al.*, 1991; Reid *et al.*, 1995).

All those parameters which were included in the three final multivariable models were investigated further on an individual level using receiver operating characteristic (ROC) curves. ROC curves provided a simple means of comparing how well each test parameter classified cattle into the appropriate group (Görög, 1994). In the context of this study, the tests were to differentiate between cattle with acute inflammatory processes and cattle with chronic inflammatory processes, and given that acute inflammatory processes may be regarded as more serious, a "positive test result" indicated acute inflammatory processes for the purposes of the calculations. A test result was deemed "positive" when the parameter value for a case was at or above a selected cut-off point. A test result was deemed "negative" when the parameter value for a case did not exceed the selected cut-off point. Sensitivity represented the proportion of animals with acute inflammatory processes which tested positive. Specificity represented the proportion of animals with chronic inflammatory processes which tested negative. For each parameter, the sensitivity and specificity for an appropriate range of cut-off points, incorporating the minimum and maximum dataset values, were calculated. The sensitivity and specificity changed, depending on the chosen value for the cut-off point.

The changes in sensitivity and specificity caused by altering the cut-off points were then represented graphically using ROC curves. The ROC curves were generated by plotting the true-positive ratio (i.e. sensitivity) against the false-positive ratio (i.e. 1-specificity) (Christensen, 1992; Young, 1992; Henderson, 1993; Jensen, 1994). The resulting ROC curves were compared visually, with the curve situated in the uppermost left-hand region of the graph representing the test which best discriminated between the two groups (Møller-Peterson, 1992; Henderson, 1993; Jensen, 1994).

7.4 RESULTS

7.4.1 Descriptive statistics

Tables 7-1, 7-2 and 7-3 show summary statistics for each of the 29 clinical laboratory parameters obtained, with clinical biochemistry, clinical haematology and acute phase protein parameters depicted respectively. Simple comparison of the minimum, maximum and mean values for the two groups suggested that the results for acute cases and chronic cases may be different. For example, Table 7-3 shows that the values obtained for the acute phase proteins, SAA, HP and AGP, were higher in the acutely ill cattle than in the chronically ill. However, similar examination of Table 7-2 showing the haematology results yielded less convincing results. Table 7-1 shows that differences between the clinical biochemistry results in acute and chronic cases varied from parameter to parameter.

Laboratory parameter	Units	Disease status	No. of cases	Min.	Max.	Mean	St. dev.
Urea	mmol/l	Acute	29	2.2	35.4	9.74	8.75
		Chronic	47	1.6	40.0	7.20	7.89
Sodium	mmol/l	Acute	29	108	142	128.6	9.3
		Chronic	48	114	146	133.2	6.6
Potassium	mmol/l	Acute	28	2.0	7.3	4.01	0.96
		Chronic	48	1.6	6.7	4.30	1.03
Chloride	mmol/l	Acute	29	65	117	92.2	12.0
		Chronic	48	57	105	92.9	9.3
Calcium	mmol/l	Acute	28	1.89	2.83	2.415	0.224
		Chronic	48	1.90	2.84	2.305	0.197
Magnesium	mmol/l	Acute	28	0.36	1.59	0.692	0.276
		Chronic	48	0.31	1.18	0.680	0.203
Phosphate	mmol/l	Acute	28	0.25	4.70	1.988	0.937
		Chronic	48	1.21	3.44	2.136	0.543
Creatinine	µmol/l	Acute	29	62	450	146.8	106.7
		Chronic	48	47	1075	144.0	170.5
Bilirubin	µmol/l	Acute	25	0	19	5.3	5.7
		Chronic	45	0	48	6.5	8.7
AP	u/l	Acute	28	49	484	190.6	127.6
		Chronic	48	56	732	215.5	132.4
AST	u/l	Acute	29	38	312	104.4	59.9
		Chronic	48	31	1138	139.4	167.5
TP	g/l	Acute	29	65	117	91.3	13.3
		Chronic	48	50	110	76.2	12.7
Albumin	g/l	Acute	28	17	43	27.8	6.3
		Chronic	48	15	43	26.4	5.9
Globulin	g/l	Acute	28	37	98	63.6	15.8
		Chronic	48	22	89	49.6	14.7
GGT	u/l	Acute	26	9	386	47.1	76.5
		Chronic	43	1	911	78.4	160.0
GLDH	u/l	Acute	22	0	170.0	36.90	48.90
		Chronic	36	0	164.0	29.83	37.98

Table 7-1 Descriptive statistics for the biochemistry parameters measured in up to 81 cattle cases which presented to the University of Glasgow Veterinary School. Results for cases classified as having acute or chronic inflammatory processes are shown separately.

Laboratory parameter	Units	Disease status	No. of cases	Min.	Max.	Mean	St. dev.
RBC	$x10^{12}/l$	Acute	31	3.42	16.40	6.711	2.613
		Chronic	48	1.91	15.50	8.207	3.075
Hb	g/dl	Acute	30	6.2	20.0	11.06	3.15
		Chronic	48	4.3	20.0	10.90	3.03
PCV	l/l	Acute	31	18.8	50.8	30.15	7.96
		Chronic	48	14.1	53.0	31.05	8.10
WBC	$x10^{9}/l$	Acute	31	2.0	54.0	12.17	9.93
		Chronic	50	2.7	42.2	12.02	7.95
BPMN	%	Acute	31	0.0	52.0	6.73	12.30
		Chronic	50	0.0	13.5	1.26	3.01
PMN	%	Acute	31	0.5	82.0	49.49	22.03
		Chronic	50	8.0	91.0	50.83	20.95
LYM	%	Acute	31	8.0	95.0	32.83	19.46
		Chronic	50	7.5	83.0	40.04	20.44
MON	%	Acute	31	0.0	22.0	4.85	5.00
		Chronic	50	0.0	16.0	4.79	3.75
ESO	%	Acute	31	0.0	8.0	0.95	2.04
		Chronic	50	0.0	5.0	0.56	1.13
BASO	%	Acute	31	0.0	1.5	0.08	0.32
		Chronic	49	0.0	1.0	0.06	0.19

Table 7-2 Descriptive statistics for haematology parameters measured in 81 cattle cases which presented to the University of Glasgow Veterinary School. Results for cases classified as having acute or chronic inflammatory processes are shown separately.

Laboratory parameter	Units	Disease status	No. of cases	Min.	Max.	Mean	St. dev.
SAA	mg/l	Acute	31	21.4	212.6	74.27	45.80
		Chronic	50	0.0	30.4	11.73	9.51
HP	g/l	Acute	31	0.06	3.06	1.476	1.166
		Chronic	50	0.06	2.20	0.374	0.594
AGP	mg/l	Acute	28	230	1500	1101.4	439.5
		Chronic	50	190	1500	815.2	446.9

Table 7-3 Descriptive statistics for the results of acute phase proteins measured in 81 cattle cases which presented to the University of Glasgow Veterinary School. Results for cases classified as having acute or chronic inflammatory processes are shown separately.

7.4.2 Two-sample test results

Univariable screening using Student's two-sample t-tests was performed for each of 28 parameters. Globulin was not included because it had been derived directly from total protein and albumin. The results are displayed in Table 7-4. The parameters are ordered by most significantly associated with disease status first (SAA, total protein, and haptoglobin) through to those not significantly associated with disease status (creatinine, white blood cell count and monocyte count, and so on). From the two-sample test results, a total of eight parameters showed a significant difference between the two groups at $P<0.1$. These parameters were SAA, total protein, HP, AGP, BPMN, RBC, sodium and calcium. All the parameters significant at $P<0.1$ were then used to perform multivariable logistic regression analysis.

Laboratory Parameter	Mean Acute	Chronic	P-value
SAA	74.27	11.73	<0.0001
Total protein	91.3	76.2	<0.0001
HP	1.476	0.374	<0.0001
AGP	1101.4	815.2	0.0082
BPMN	6.73	1.26	0.0210
RBC	6.711	8.207	0.0230
Sodium	128.62	133.23	0.0240
Calcium	2.4154	2.3046	0.0350
LYM	32.83	40.04	0.1200
AST	104.4	139.4	0.1900
Urea	9.74	7.20	0.2100
Potassium	4.007	4.304	0.2100
GGT	47.1	78.4	0.2800
Albumin	27.8	26.4	0.3300
ESO	0.952	0.560	0.3300
AP	190.6	215.5	0.4200
Phosphate	1.988	2.136	0.4500
Bilirubin	5.32	6.49	0.5000
GLDH	36.90	29.83	0.5700
PCV	30.15	31.05	0.6300
BASO	0.0821	0.0612	0.7400
PMN	49.49	50.83	0.7900
Chloride	92.24	92.87	0.8100
Hb	11.063	10.900	0.8200
Magnesium	0.6918	0.6796	0.8400
Creatinine	146.8	144.0	0.9300
WBC	12.17	12.02	0.9400
MON	4.853	4.788	0.9500

Table 7-4 Results of the Student's two-sample t-tests carried out to assess whether the parameter results obtained in 31 cattle with acute inflammatory processes were significantly different from results obtained in 50 cattle with chronic inflammatory processes.

7.4.3 Multivariable logistic regression models

7.4.3.1 Clinical biochemistry parameters

Multivariable logistic regression analysis involving only clinical biochemistry parameters was run with those parameters which were found to be significant using two-sample testing, namely, total protein, sodium and calcium. One of the advantages of reducing the number of variables which were included in the analysis was to increase the total number of cases which were used in defining the final model. Table 7-5 shows the Sx output displaying the final model, detailing the coefficient and associated p-value for each variable. Total protein and calcium were concluded as being the clinical biochemistry parameters which best classified the cattle into appropriate groups. Sodium failed to significantly improve the model.

Predictor variables	Coefficient	Std error	Coeff/SE	P
Constant	-13.9734	4.1235	-3.39	0.0007
TP	0.0871	0.0234	3.72	0.0002
CA	2.5999	1.4428	1.80	0.0716
Deviance	75.72			
P-value	0.3908			
DF	73			

Table 7-5 Multivariable logistic regression model containing parameters total protein and calcium. Total protein and calcium were the clinical biochemistry parameters which, in combination, best classified cattle as having acute or chronic inflammation.

Hosmer-Lemeshow goodness of fit statistics are shown in Table 7-6, the contents of which were used to calculate sensitivity and specificity at various probability cut-points. The Hosmer-Lemeshow statistic of 6.85, with an associated p-value of 0.5524 indicated that the model fitted the observed data well (Hosmer and Lemeshow, 1989). Table 7-7 shows a worked example of the calculation of sensitivity and specificity of the model using the predicted probability cut-off of 0.5. Table 7-8 shows the sensitivity and specificity of the model at each cut-point, with Figure 7-1 depicting a graphical representation. It was concluded that the multivariable logistic regression model developed using the clinical biochemistry parameters to differentiate between cattle with

acute and chronic inflammation, contained the variables total protein and calcium, and had a sensitivity of 57.1% and a specificity of 85.4% at the predicted probability of 0.5.

Code		Fixed Cut Points										
		0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	Total
1	Obs	0	3	4	1	4	5	2	3	3	3	28
	Exp	0.6	2.2	2.6	2.4	4.1	3.9	3.2	3.8	2.5	2.8	28
0	Obs	11	13	6	6	5	2	3	2	0	0	48
	Exp	10.4	13.8	7.4	4.6	4.9	3.1	1.8	1.2	0.5	0.2	48
	Total	11	16	10	7	9	7	5	5	3	3	76

Hosmer-Lemeshow Statistic	6.85
P-value	0.5524
Degrees of Freedom	8

Table 7-6 Hosmer-Lemeshow goodness of fit statistics for the multivariable logistic regression model which included total protein and calcium, the clinical biochemistry parameters which, in combination, best classified cattle as having acute or chronic inflammation.

Predicted probability	Observed number of cases		
	Acute cases	Chronic cases	Totals
P>0.5	16	7	23
P≤0.5	12	41	53
Totals	28	48	76
Sensitivity	16/28 = 57.1%		
Specificity	41/48 = 85.4%		

Table 7-7 Calculation of the sensitivity and specificity of the multivariable model developed using the clinical biochemistry parameters, using an example of predicted probability cut-off point of 0.5 for the final model which included total protein and calcium only.

	Fixed Cut Points								
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Sensitivity (%)	100	89.3	75.0	71.4	57.1	39.3	32.1	21.4	10.7
Specificity (%)	22.9	50.0	62.5	75.0	85.4	89.6	95.8	100	100

Table 7-8 Sensitivity and specificity of the model which included total protein and calcium as the clinical biochemistry parameters which best classified the cattle into the appropriate group.

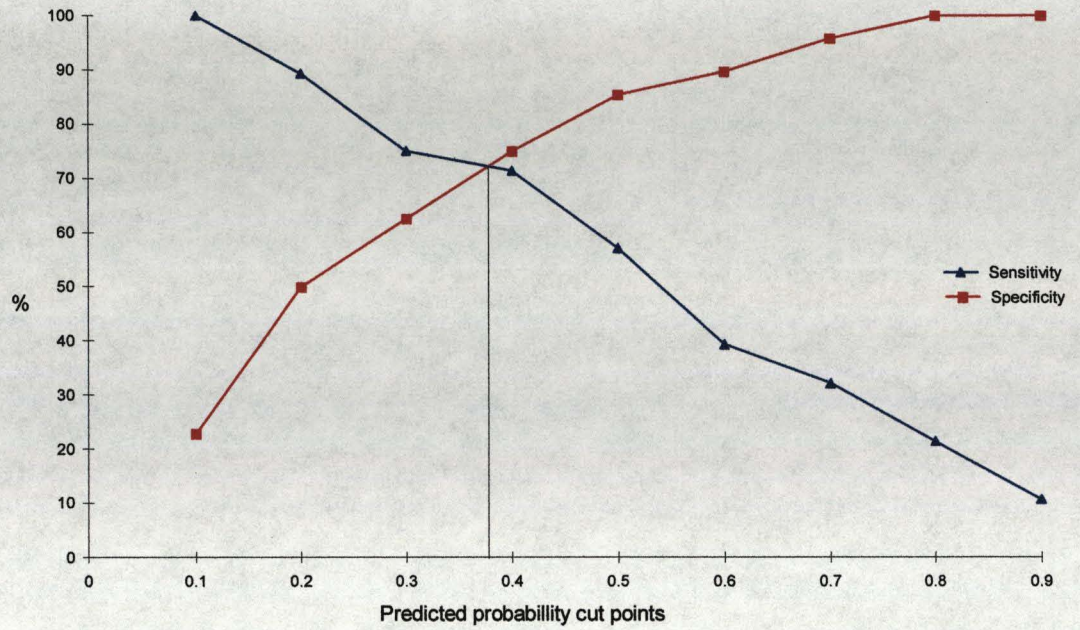


Figure 7-1 Graphical representation of sensitivity and specificity of model with total protein and calcium as clinical biochemistry parameters which best classified cattle into 'acute' and 'chronic' groups.

7.4.3.2 Clinical biochemistry and haematology parameters

Univariable screening indicated that for five clinical biochemistry and haematology parameters there was a significant difference between the mean value for the acute and chronic groups. Total protein, BPMN, RBC, sodium and calcium were included for multivariable analysis. Following stepwise logistic regression analysis, a multivariable model which included four parameters, total protein, red blood cell count, band polymorphonuclear leukocytes and calcium, was obtained. Again, sodium did not contribute to the model. Table 7-9 shows the model output from Sx, detailing the coefficient and associated p-value for each variable.

Predictor variables	Coefficient	Std error	Coeff/SE	P
Constant	-12.1131	4.2943	-2.82	0.0048
TP	0.0876	0.0253	3.46	0.0005
RBC	-0.3738	0.1503	-2.49	0.0129
BPMN	0.1397	0.0727	1.92	0.0547
CA	2.7851	1.5615	1.78	0.0745
Deviance	59.58			
P-value	0.8083			
DF	70			

Table 7-9 Logistic regression model, developed using individually significant clinical biochemistry and haematology parameters, containing total protein, red blood cell count, band polymorphonuclear leukocytes and calcium, which, in combination, best classified 81 GUVS cattle as having acute or chronic inflammation.

Table 7-10 shows the Hosmer-Lemeshow goodness of fit statistics, and displays the observed and expected cases achieved at different fixed cut points. The Hosmer-Lemeshow statistic of 10.55, with an associated p-value of 0.2284 indicated that the model fitted the observed data reasonably well. Table 7-11 shows the sensitivity and specificity of the model at the different cut points, calculated using the method outlined earlier in Table 7-7. Figure 7-2 is a graphical representation of the specificity and sensitivity of the multivariable model. It was concluded that the multivariable model developed using clinical biochemistry and haematology parameters to differentiate between cattle with acute and chronic inflammation, contained the variables total protein, red blood cell count, percentage band polymorphonuclear leukocytes and calcium, and had a sensitivity of 60.7% and a specificity of 89.4% at a predicted probability cut-point of 0.5.

Code		Fixed Cut Points									
		0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	Total
1	Obs	0	2	1	3	5	1	1	2	6	7	28
	Exp	0.8	1.6	2.3	1.7	3.1	0.5	0.7	3.7	6.8	6.8	28
0	Obs	20	9	9	2	2	0	0	3	2	0	47
	Exp	19.2	9.4	7.7	3.3	3.9	0.5	0.3	1.3	1.2	0.2	47
	Total	20	11	10	5	7	1	1	5	8	7	75

Hosmer-Lemeshow Statistic	10.55
P-value	0.2284
Degrees of Freedom	8

Table 7-10 Hosmer-Lemeshow goodness of fit statistics for the multivariable logistic regression model which included haptoglobin, total protein, red blood cell count and calcium, the clinical biochemistry and haematology parameters which, in combination, best classified cattle as having acute or chronic inflammation.

	Fixed Cut Points								
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Sensitivity (%)	100	92.9	89.3	78.6	60.7	57.1	53.6	46.4	25.0
Specificity (%)	42.6	61.7	80.9	85.1	89.4	89.4	89.4	95.7	100

Table 7-11 Sensitivity and specificity of the multivariable model which included total protein, band polymorphonuclear leukocytes, red blood cell count and calcium.

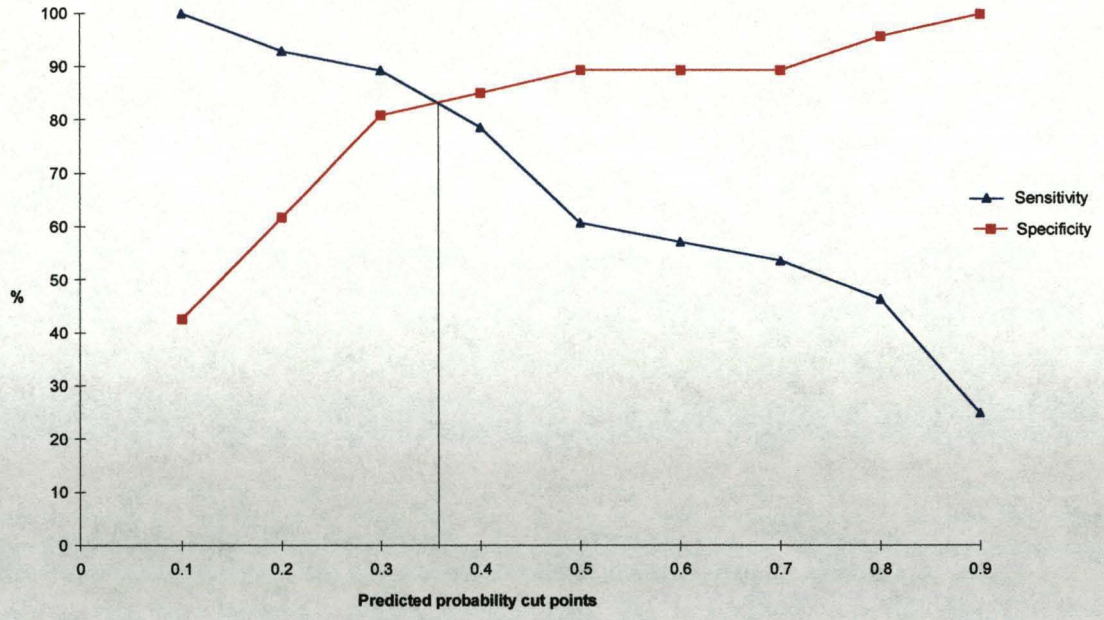


Figure 7-2 Graphical representation of sensitivity and specificity of the model which included total protein, band polymorphonuclear leukocytes, red blood cell count and calcium, the combination of clinical biochemistry and haematology parameters which best classified cattle into acute and chronic groups.

7.4.3.3 Clinical biochemistry, haematology and acute phase protein parameters

Following introduction of the acute phase parameters, SAA, AGP and HP to the multivariable analysis, the model appeared unstable and failed to converge after the parameter SAA was fitted. The reason for this became clear when the distributions of the results within each of the acute and chronic groups were ascertained. Figure 7-3 shows the distribution of the SAA results for the cattle, with the results for the acute and chronic groups depicted separately. There is very little overlap of the two sets of results. This may be compared with Figure 7-4, which shows the total protein results which demonstrate substantial overlap of results between the two groups. In fact, when one ill-fitting SAA case was excluded there was complete separation of the two groups. This suggested that SAA alone was sufficient to classify all but one of the cases into the appropriate group.

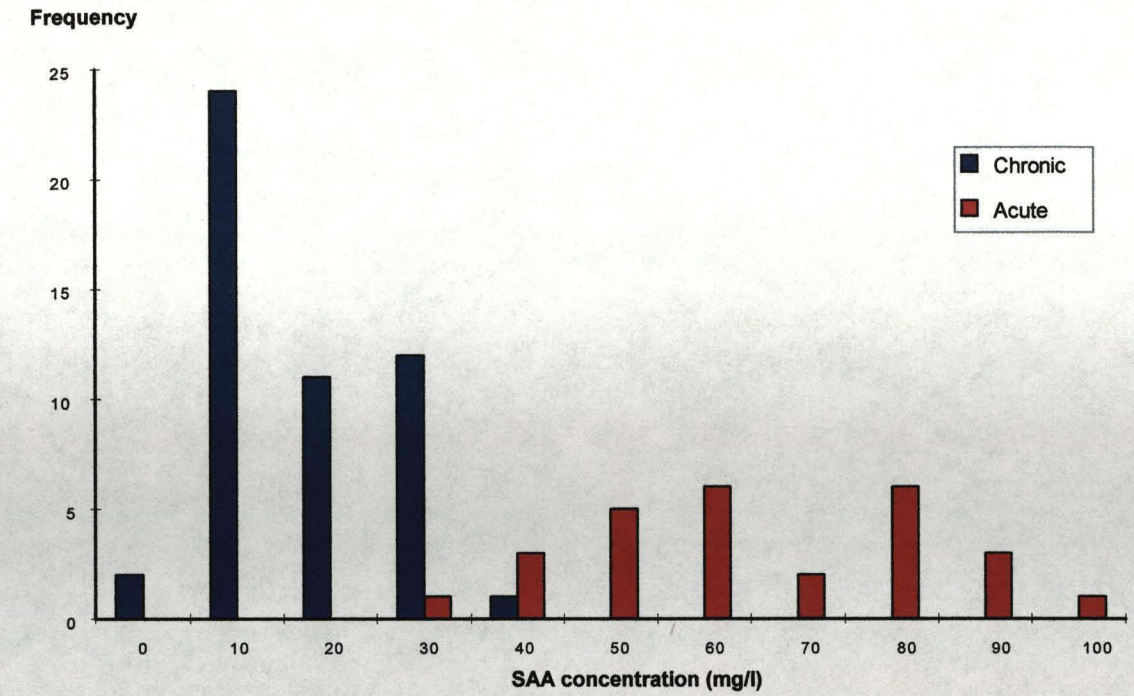


Figure 7-3 Distribution of serum amyloid-A results from 81 cattle cases which presented to the University of Glasgow Veterinary School. Results for cases classified as having acute or chronic inflammatory processes are shown separately.

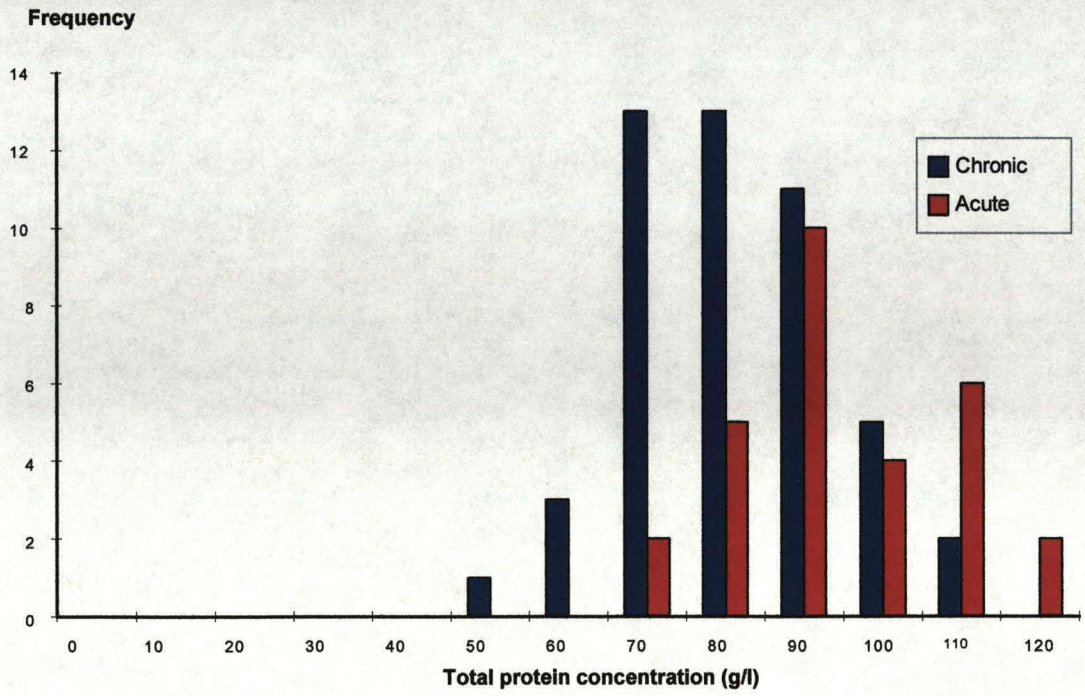


Figure 7-4 Distribution of total protein results from 81 cattle cases which presented to the University of Glasgow Veterinary School. Results for cases classified as having acute or chronic inflammatory processes are shown separately.

This was substantiated further, when, in accordance with the models derived using only the clinical biochemistry and haematology results, a model containing only one variable, SAA, was assessed as the parameter out of the total twenty-nine clinical biochemistry, haematology and acute phase parameters which best classified the cattle into acute and chronic groups. All the available cases were included for the analysis, a total of 81; 31 classified as acute, and 50 classified as chronic. Table 7-12 details the coefficient and p-value associated with SAA in the model. Observed and predicted number of cases are given at several probability cut-off points (Table 7-13). Table 7-14 shows the sensitivity and specificity of the model calculated at the different probability cut points, and Figure 7-5 shows a graphical representation of the sensitivity and specificity of the SAA model.

Predictor variables	Coefficient	Std error	Coeff/SE	P
Constant	-11.4300	4.0331	-2.83	0.0046
SAA	0.3563	0.1310	2.72	0.0065
Deviance	13.00			
P-value	1.0000			
DF	79			

Table 7-12 Logistic regression model containing serum amyloid A only, the clinical laboratory parameter which best classified 81 GUVS cattle into acute and chronic groups with respect to inflammatory processes.

Code		Fixed Cut Points										
		0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	Total
1	Obs	1	0	0	0	0	0	0	1	2	27	31
	Exp	0.3	0.4	0.6	0.4	0.0	0.0	0.0	0.7	1.7	26.9	31
0	Obs	44	3	2	1	0	0	0	0	0	0	50
	Exp	44.7	2.6	1.4	0.6	0.0	0.0	0.0	0.3	0.3	0.1	50
	Total	45	3	2	1	0	0	0	1	2	27	81

Hosmer-Lemeshow Statistic	-
P-value	-
Degrees of Freedom	-

Table 7-13 Hosmer-Lemeshow goodness of fit statistics were not calculated for the logistic regression model which contained SAA only as the parameter which best classified 81 cattle seen at GUVS as having acute or chronic inflammation. This was due to the sparsity of data leading to a large number of zero cells.

	Fixed Cut Points								
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Sensitivity (%)	96.8	96.8	96.8	96.8	96.8	96.8	96.8	93.5	87.1
Specificity (%)	88.0	94.0	98.0	100	100	100	100	100	100

Table 7-14 Sensitivity and specificity of the model which included Serum Amyloid A only as the parameter which best classified 81 cattle into appropriate groups with respect to inflammatory status.

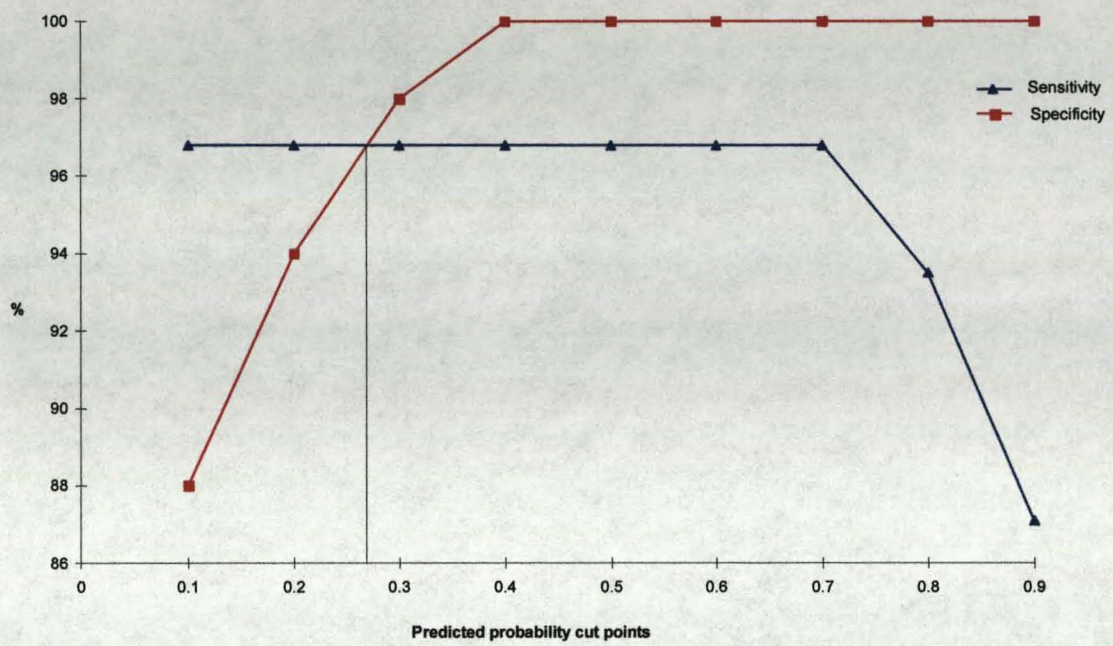


Figure 7-5 Graphical representation of sensitivity and specificity of the model which included Serum Amyloid-A only, developed using clinical biochemistry, haematology and acute phase protein parameters.

It was concluded that the SAA model for differentiating between acute and chronic groups had an acceptable sensitivity of 97% and a specificity of 100% at a predicted probability cut point of 0.5.

7.4.4 Receiver operating characteristic curves

Receiver operating characteristic curves were constructed for each of the parameters which appeared in the multivariable models. Table 7-15 demonstrates the calculation of

the sensitivity and specificity of SAA for differentiating between cattle with acute and chronic inflammation, with a cut-off value of 27 mg/l shown as an example.

		Acute inflammation		
		Y	N	Total
Test Positive	Y	30	4	34
	N	1	46	47
	Total	31	50	81

Sensitivity = (30/31) = 96.8%
Specificity = (46/50) = 92.0%

Table 7-15 Calculation of the sensitivity and specificity of serum amyloid-A used to differentiate between cattle with acute and chronic inflammation, with a cut-off value of 27 mg/l shown as an example, for 81 cattle which presented to GUVS.

Tables for each of the selected laboratory parameters detailing the variation in sensitivity and specificity as the cut-off values change are given in Appendix VI. ROC curves were constructed for total protein concentration, calcium concentration, red blood cell count, percent band polymorphonuclear leukocytes and serum amyloid-A concentration, as shown in Figure 7-6. Serum amyloid A was the parameter whose ROC curve was situated most towards the uppermost left hand quadrant of the graph, indicating that it is likely to be superior to the other tests with respect to correctly classifying animals into the appropriate group of inflammation, as discussed in 7.3.2.

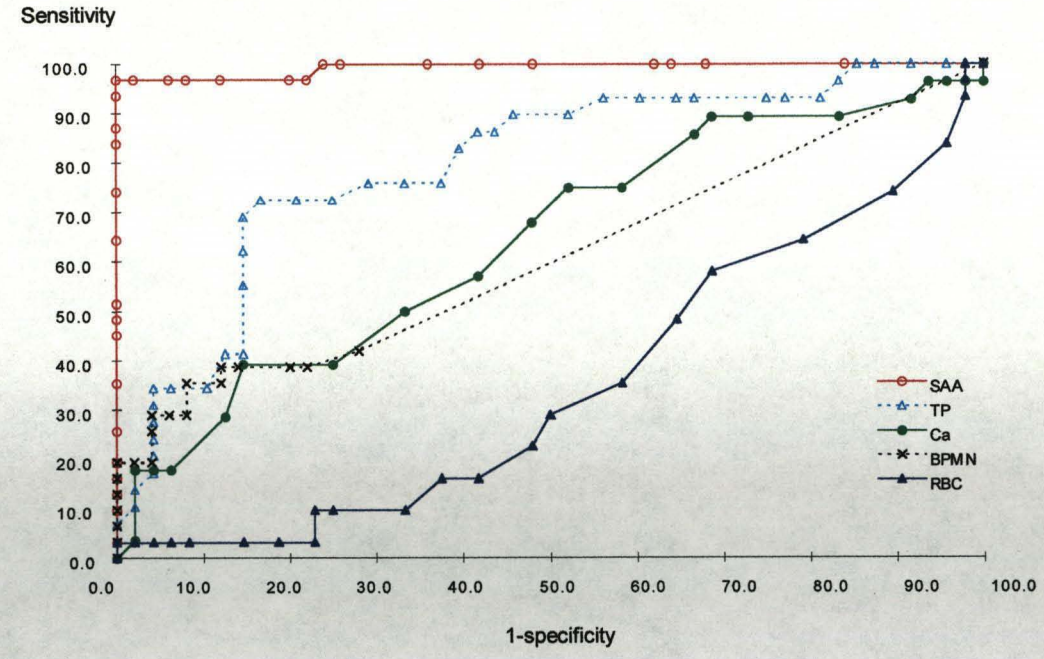


Figure 7-6 Relative operating characteristic (ROC) curves for serum amyloid A (SAA), total protein (TP), calcium, band polymorphonuclear leukocytes (BPMN) and red blood cell count (RBC) used to differentiate between a total of 81 cattle with acute or chronic inflammation.

7.5 DISCUSSION

7.5.1 Summary of findings

This study has resulted in the identification of laboratory tests which may be used to differentiate between cattle which have acute or chronic inflammatory processes. The study was undertaken in three phases, first investigating clinical biochemistry parameters alone; second, investigating a combination of clinical biochemistry and haematology parameters; and finally, investigating a combination of clinical biochemistry, haematology and acute phase protein parameters.

Following multivariable logistic regression analysis involving only individually significant clinical biochemistry parameters, total protein and calcium were identified as being the clinical biochemistry parameters which best classified the cattle into appropriate groups. From descriptive summaries of the acute and chronic groups, it was ascertained that the mean total protein concentration for the cattle with chronic inflammation was lower than that for the cases with acute inflammation. Proteins play an integral role in numerous physiological processes, and their plasma concentration is

known to be altered by a variety of different conditions. For example, prolonged liver disease will ultimately result in hypoalbuminaemia due to decreased albumin synthesis in the liver; nephropathies and enteropathies can also result in hypoalbuminaemia, but as a result of increased excretion. Hyperproteinaemia may be a reflection of hypergamma-globulinaemia, often in response to chronic antigenic stimulation (Kerr, 1989). General inflammation, through alterations in capillary membrane permeability can also cause alteration in plasma protein concentration (Eades and Bounous, 1997). Thus a number of factors may affect plasma protein concentrations, and highlight its potential importance in association with inflammatory processes. In relation to plasma calcium, this parameter is important in many physiological processes, and for this reason, its concentration is normally maintained within a relatively narrow range (Carlson, 1990), and large increases or decreases in serum calcium concentration are usually the result of failure in the normal mechanisms of calcium homeostasis. From descriptive statistics pertaining to the cattle with acute or chronic inflammatory processes, it was ascertained that the mean calcium concentration for the chronic cases was lower than that for the cases with acute inflammation. Hypocalcaemia is more commonly encountered than hypercalcaemia, and has a number of causes including as hypoalbuminaemia, parturient paresis and chronic renal failure (Kerr, 1989).

During the second phase of the study, individually significant clinical biochemistry and haematology parameters were input for multivariable logistic regression analysis. A combination of four parameters, total protein, red blood cell count, band polymorphonuclear leukocytes and calcium, were identified as those which best classified the cases into acute and chronic groups. Both total protein and calcium remained within the model following the introduction of the haematology parameters, emphasising the importance of these parameters in differentiating between the two groups of cattle. Descriptive statistics for red blood cell count indicated that the mean count in cases with acute inflammation was lower than the mean count in cases with chronic inflammation. This was in keeping with the negative coefficient associated with this parameter in the multivariable model (Table 7-9) which indicated that as red blood cell count went down, the case was more likely to be classified as acute. Red blood cell count may be altered by a variety of conditions. It may be lowered by one of three mechanisms: blood loss, increased rate of destruction and impaired production. Blood loss could be as a result of a traumatic incident, and therefore may be associated with acute inflammation, although

it may also be due to a chronic gastro-enterological disorder, such as parasitism; increased rate of destruction in haemolytic anaemias may be acute or chronic in nature, depending on the cause of the anaemia; and, chronic renal disease may impair red cell production, because of the lack of erythropoietin (Finco, 1997). On the other hand, erythrocytosis may be relative or absolute. If it were relative, it may be due to the dehydrated state of the animal, often apparent in chronic disease. Absolute erythrocytosis may be secondary to an increase in erythropoietin, the most common cause of which is hypoxia resulting from cardiac insufficiency or chronic pulmonary disease (Meyer *et al.*, 1992). From this brief outline of pathology associated with changing red blood cell counts, its relevance to differentiating between cattle with acute and chronic inflammation may be realised. Band polymorphonuclear leukocytes are immature forms of neutrophils. Neutrophils are the most common type of white cell in the blood, and constitute 40 to 75 per cent of circulating leukocytes. The principle function of neutrophils is to engulf invading micro-organisms, particularly bacteria (Swenson, 1993). When the demand for neutrophils becomes high, such as in acute inflammation, immature forms are also released from the bone marrow (Wheater *et al.*, 1987). This highlights the importance of BPMN in distinguishing between cattle with acute and chronic inflammation, in that in acute inflammation, more immature band cells are likely to be in the circulation. This is supported by the descriptive statistics pertaining to BPMN in the 81 cattle cases investigated, the mean value for BPMN in acute cases being higher than for the chronic cases.

Following inclusion of the three acute phase proteins in the stepwise multivariable logistic regression analysis, together with the other individually significant clinical biochemistry and haematology parameters, the model failed to converge. The situation arose due to the inadequate overlap of the SAA results from the acute and chronic groups, such that one ill-fitting case prevented complete separation of the groups (Knox *et al.*, 1997). It was concluded that, of the 29 laboratory parameters, the one which best differentiated between those animals with acute or chronic inflammatory processes was the acute phase protein serum amyloid-A. This determination was supported by comparison of the sensitivity and specificity of the three logistic regression models: The SAA only model was both more sensitive and specific than the previous multivariable model which had been derived using only the routine laboratory parameters.

Further support for the value of SAA as a parameter for differentiating between cattle with acute and chronic inflammation was derived from ROC curve analysis. ROC curves for each of total protein, calcium, RBC, BPMN and SAA were constructed and compared within one graph. SAA was the parameter located within the uppermost left-hand corner of the graph, indicating that is was the test which best differentiated between the two groups (7.3.2).

In 1989 Serum Amyloid A was identified as a protein which was of importance in the acute phase response in cattle (Boosman *et al.*, 1989), and it has since been studied in detail, along with several other acute phase proteins, caeruloplasmin, fibrinogen, haptoglobin, α-1-antitrypsin and α-1-acid glycoprotein (Young *et al.*, 1995). SAA is a positive acute phase protein whose concentration can increase rapidly up to 1000-fold (Gruys *et al.*, 1994). It was not until 1993 that a method for the accurate quantification of SAA in serum was described (Horadagoda *et al.* 1993). There has been increasing interest in the use of acute phase proteins as indicators of infection or inflammation and several groups are currently working on inexpensive and rapid, animal-side assays that may be used at the time of slaughter (Saini and Webert, 1991; Sheffield *et al.*, 1994; Francisco *et al.*, 1996). The findings of the present study emphasise the potential value of being able to quantify SAA in cattle, and highlight the importance of this parameter in the recognition of acute inflammatory processes.

7.5.2 Multivariable logistic regression analysis

The aim of this study was to identify the parsimonious combination of clinical laboratory variables which best classified cattle into appropriate groups with respect to inflammation status. Multivariable logistic regression analysis was deemed appropriate because there were two possible outcomes, acute or chronic inflammation; and, by employing a step-wise procedure, a model which used a combination of explanatory variables to classify the dependent variable could be developed. The importance of univariable pre-screening was that the parameters of likely value were identified at an early stage in the analysis. Initial screening by performing two-sample tests prior to multivariable logistic regression analysis therefore reduced the number of explanatory variables introduced to the model. Although step-wise logistic regression analysis also cuts down the number of parameters in the final model, more cases are likely to be

discarded from the analysis if there are many variables with missing data. BMDP automatically removes all cases which have any missing data, and so if the number of variables is reduced, more cases are likely to have complete sets of data, such that ultimately the total number of cases which may be included for analysis is greater, and thus any model derived more reliable (Reeves *et al.*, 1990).

For this study, multivariable logistic regression analysis was run on three datasets, one derived from clinical biochemistry parameters alone; one derived from clinical biochemistry and haematology parameters; and one derived from clinical biochemistry, haematology and acute phase protein parameters. When multivariable logistic regression analysis was run using the third dataset, the model in BMDP failed to converge if any variables additional to SAA were included. As detailed in *7.4.3.3*, this was because of inadequate overlap of the SAA results between the acute and chronic cases. This suggested that multivariable logistic regression analysis may not have been appropriate in this situation, where inspection of the results for one variable, SAA, was clearly sufficient to differentiate almost entirely correctly between the two groups.

7.5.3 Receiver operating characteristic curves

Generation of ROC curves provided a simple means of comparing how well each test parameter classified cattle into the appropriate group. ROC curves are commonly employed in clinical biochemistry testing, both in the human and the veterinary domains (Görög, 1994). The ability of a laboratory test to classify animals correctly into one of two groups is commonly assessed by sensitivity and specificity, the groups frequently representing "diseased/not diseased" and "normal/abnormal". The concept of sensitivity and specificity of laboratory tests is vital with respect to appropriate interpretation, even though it is often ignored or misunderstood by practising clinicians (Young, 1992). Application of ROC curves allowed the sensitivity and specificity of various laboratory test results to be compared in a visual manner. More sophisticated techniques can be applied to the graphs, such as calculation of the area under the curve, in order to provide a more accurate indication of parameter operation (Young, 1992; Henderson, 1993). However, simple visual assessment of the ROC curves generated in this study clearly demonstrated that SAA had a higher sensitivity and specificity than the other variables identified as key in differentiating between cattle with acute and chronic inflammatory

processes. That is, almost all the cattle under investigation could be classified appropriately on the basis of the SAA concentration.

7.5.4 Implications of findings

This study has resulted in the identification of laboratory tests which may be used to differentiate between cattle which have acute or chronic inflammatory processes. It was concluded that a single animal-side test for SAA may be capable of differentiating between cattle with acute or chronic cases, with implications for both clinical care and meat hygiene. These findings are of particular importance in two respects: meat hygiene and clinical cattle care.

7.5.4.1 Meat hygiene

In the wake of recent public crises, the reputation of the UK meat industry has come under scrutiny. Proposals for a Food Standards Agency outlined by the Government reflect the scale of the problem (Vet Record, 1997f). In the current climate, it is important that appropriate means of minimising risks to the consumer are established. Inflammation encompasses a series of complex changes which occur in an animal as a result of insult which has been insufficient to cause necrosis of the tissue (Gracey and Collins, 1992). There are a number of causes of inflammation which include toxins, micro-organisms, chemicals, mechanical injuries, thermal damage, immune reactions. Inflammation is the first reaction tissues undergo in an attempt to heal. Gracey and Collins (1992) state, "The type of inflammation and its stage are important considerations in meat inspection, acute inflammation in general being more serious than the chronic form". Current meat inspection procedures are weighted towards the detection of disease either in the live animal or *post mortem*. Although efficient *ante mortem* inspection markedly reduces *post mortem* condemnation, many animals may not present with overt clinical signs of disease. Gracey and Collins (1992) highlighted the necessity to differentiate between acute and chronic conditions. Acute conditions discovered at *post mortem* may require the condemnation of the whole carcass, whereas one which is chronic, and localised, may require only trimming of the appropriate area. In today's society, product quality is also of increasing importance (Bohlender, 1993). Provision of a test which may be carried out pre-slaughter to differentiate between cattle

with acute or chronic inflammatory conditions will ensure improved safety and quality of meat in the food chain, which is of increasing importance in world trade (Herrick, 1993).

7.5.4.2 Clinical care of production animals

Cattle production is a business (Fetrow *et al.*, 1985; Galligan *et al.*, 1991). However, the maintenance of the health and welfare of cattle is of the utmost importance not only to individual farmers, but also to society (Gracey and Collins, 1992). As cattle care may be conducted on a herd basis, a simple means of identifying those animals which may have acute or chronic inflammatory processes would be of value in current veterinary practice (Young *et al.*, 1995). Such animals could be removed from the herd, if necessary, and treated promptly and appropriately. This would help reduce economic loss through unwell animals, and through unnecessary treatment of healthy animals within a herd.

These aspects relating to meat hygiene and cattle care highlight the requirement for the development of a simple technique which may be carried out practically and economically for the quantification of SAA concentration.

In comparison to Chapters 4, 5 and 6, this chapter has described a smaller, focused study, in which a subset of the GUVS cattle referral population was investigated. It has thus highlighted the potential for the GUVS database to be utilised in a different way, that is, for defined investigations. However, it is interesting to note that neither the inflammation status, nor the concentrations of the acute phase protein parameters were regularly recorded in the hospital database system. This has emphasised the requirement for standardisation of data entry, whether clinical or laboratory oriented, in order that future epidemiological studies be facilitated. Nevertheless, the results of this study were of potential importance, and, as is also true of the results derived from interrogation of the hospital population, outlined in Chapters 4 and 5, a means for readily conveying the findings to interested parties is important. In this respect, Chapter 8 describes the development of a biochemistry decision support system, based on the results derived within Chapters 4 and 5.

CHAPTER VIII

DEVELOPMENT OF A DECISION SUPPORT SYSTEM

CHAPTER VIII

DEVELOPMENT OF A DECISION SUPPORT SYSTEM

"Laboratories produce data rather than information."

McNair and Brender (1990)

8.1 BACKGROUND

Throughout this thesis, raw data have been interrogated using different statistical approaches with the ultimate aim of providing useful information. In particular, Chapters 4 and 5 discussed the use of data from within the University of Glasgow Veterinary School hospital database for the development of a novel means for the objective interpretation of clinical biochemistry results. However, development of such means for interpretation can only be beneficial in the field if they are readily accessible to the clinician. To further this work, a method to convey the results of the database interrogation therefore had to be established.

8.2 INTRODUCTION

In the fields of both veterinary and human medicine knowledge about every aspect of disease is increasing at an enormous rate (Fessler, 1984a; Pollock, 1986; Thrusfield, 1995). In veterinary medicine, the situation is more complex because there are several species to consider. There are currently over 200 veterinary journals in publication (Fessler, 1884a; Pollock and Fredericks, 1988), and this, coupled with the large number of veterinary textbooks and reference manuals published yearly, emphasises the increasing wealth of knowledge in the veterinary domain. Veterinarians and human medics must be able to retain a large amount of information to ensure continued appropriate case management and patient care (Pollock and Fredericks, 1988), yet, it is becoming increasingly difficult to maintain a diversity of information which is current (White, 1987). Although individual specialisation in the veterinary field may help to address potential knowledge inadequacies, there is mounting pressure to produce measures that may assist the clinician in everyday consultation.

In conjunction to the approach described by Reid *et al.* (1996) and Mellor *et al.* (1994), detailing the development of the decision support software "EQWISE" (Equine Welfare Information System Expert), the results from the interrogation of the GUVS hospital database detailed in Chapters 4 and 5 have been used to form the basis of a biochemistry decision support system for use in veterinary medicine.

8.3 MATERIALS AND METHODS

8.3.1 Results from analysis of GUVS hospital database

The results from the analysis of the GUVS hospital database, as outlined in detail in Chapters 4 and 5, formed the basis of a biochemistry decision support system. This included the results of a percentile analysis carried out on each of the biochemistry parameters investigated, for both cattle and horses. Further information pertaining to the most common diagnoses established within the defined GUVS referral population, given that the parameter concentration lay within a stated percentile band interval, was also required for the foundation of the support system.

Tables 4.4 and 5.11 indicate the format of the percentile data supplied to an information scientist. Similarly, Tables 4.7 and 5.14 indicate the format of the diagnosis data supplied, for horses and cattle, respectively. The tables were supplied in electronic format.

8.3.2 Commissioning the support system

The programme coding for the decision support system was developed in close collaboration with an information scientist. The information scientist had been involved in the development of another veterinary application, EQWISE (Mellor *et al.* 1994), and was therefore familiar with veterinary terminology. However, given that he had no formal veterinary training, it was essential that all requirements of the decision support system be clearly defined. This facilitated his comprehension of the complex nature of the coding required to accurately reflect the results generated from the GUVS database.

In essence, the information scientist was presented with the relevant results from the interrogation of the GUVS database, various screen layout suggestions, specifications for user input requirements, and details of the requisite program output.

8.3.3 Programme coding

Using Knowledge Garden's KPWin++ development environment (Knowledge Garden Inc., USA), C++ code was produced and compiled to yield a personal computer-based windows application. Figure 8-1 shows an example of the programme coding. Of key importance in the development of the programme code was efficient data storage and indexed retrieval, to ensure accurate and efficient running of the programme.

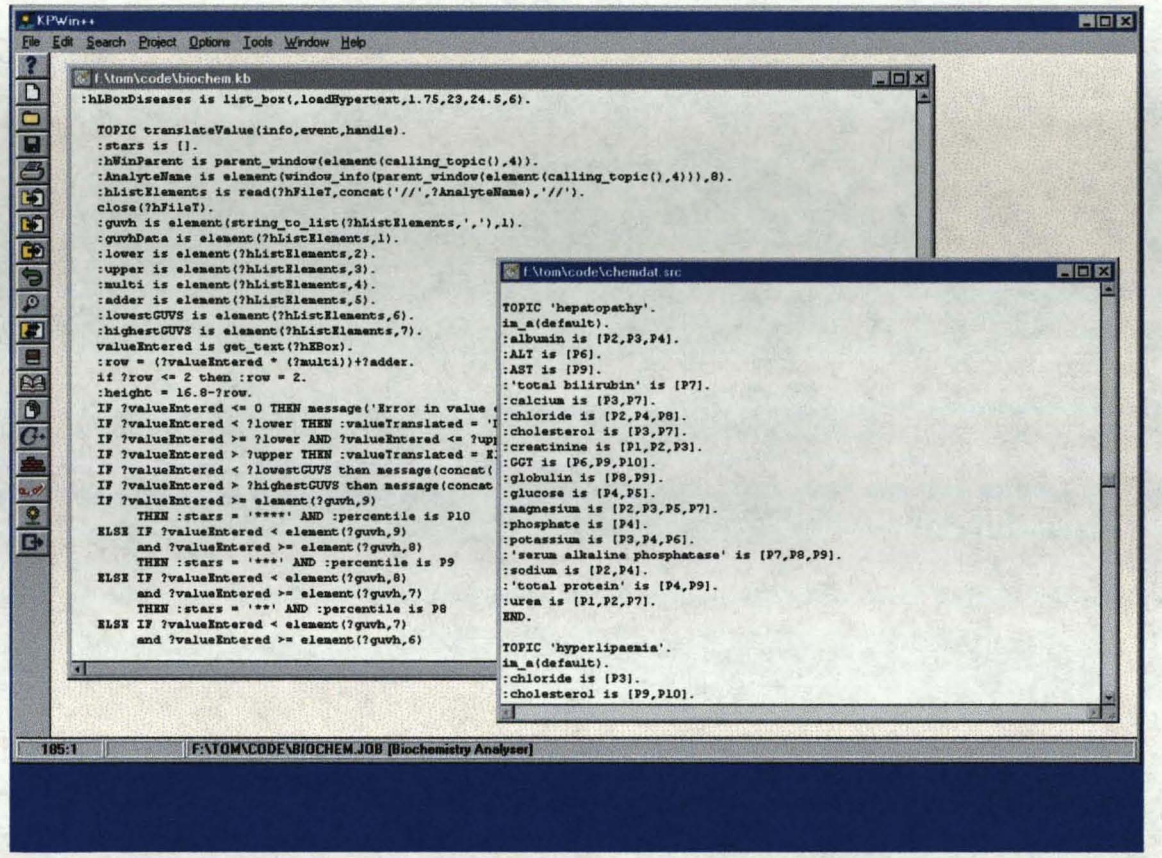


Figure 8-1 Example of KPWin++ code employed for the development of the windows-based biochemistry decision support based system.

8.4 RESULTS

The decision support system was a personal computer-based Microsoft Windows application, developed with emphasis on ease of use. As explained by the design of the system, it was termed "The Biochemical Thermometer".

8.4.1 Basic design

Potential users of the biochemistry decision support system may include veterinary practitioners, veterinary under-graduate students, referral clinicians and associated staff. Although computer-based practice management packages are increasingly popular, clinicians may be wary of computer technology in the practice environment. To overcome any possible reluctance, the design of the biochemical support system was based on a thermometer analogy, a concept familiar to all potential users. This delivery of the information provided a visual representation of a patient's plasma parameter value. Figure 8-2 displays a screen image of the thermometer design, showing a urea concentration of 2 mmol/l obtained from a horse as an example. The thermometer was used to represent the result for a new case - the higher a patient's parameter value, the greater the level of 'mercury' in the 'biochemical thermometer'. Figure 8-2 also indicates, in blue, the distribution of the results obtained from the unwell GUVS referral population, and, in green, the GUVS reference range. This novel approach of the representation of biochemistry data was simple and therefore potentially attractive to the end-user.

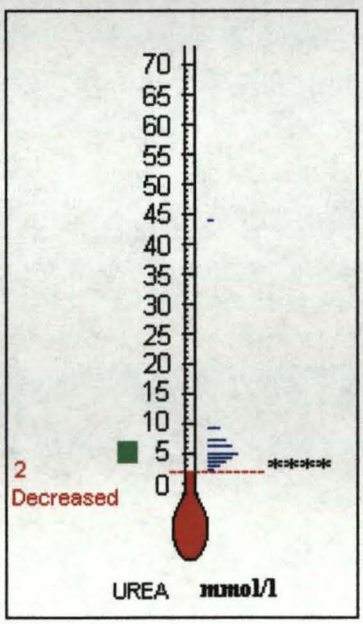


Figure 8-2 The thermometer design adopted to represent the result achieved for a new case. In this example, the horse had a urea concentration of 2 mmol/l. The blue lines on the right represent the distribution of the results previously obtained in the GUVS referral population, based on the percentile analysis. The green line on the left indicates the reference range used for urea at GUVS.

8.4.2 Functionality and decision support capabilities

Use of the Biochemical Thermometer was based on a combination of keyboard and mouse controls. The first screen, shown in Figure 8-3, prompted the user to select the biochemistry parameters in which they were interested. It was possible to enter data for up to 18 parameters for one case. Next, the user was required to enter the appropriate values achieved for the new case in question. Figure 8-4 displays the thermometers for urea, albumin and total protein, with concentrations of 2 mmol/l, 20 g/l and 60 g/l, respectively, having been entered to the system.

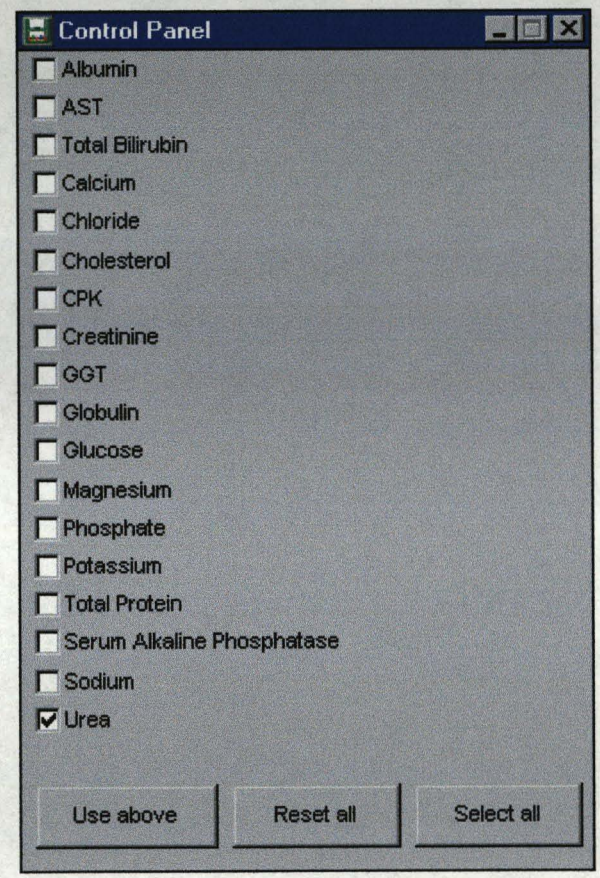


Figure 8-3 Opening screen for the decision support system, the Biochemical Thermometer, which prompts the user to select which parameters are of interest.

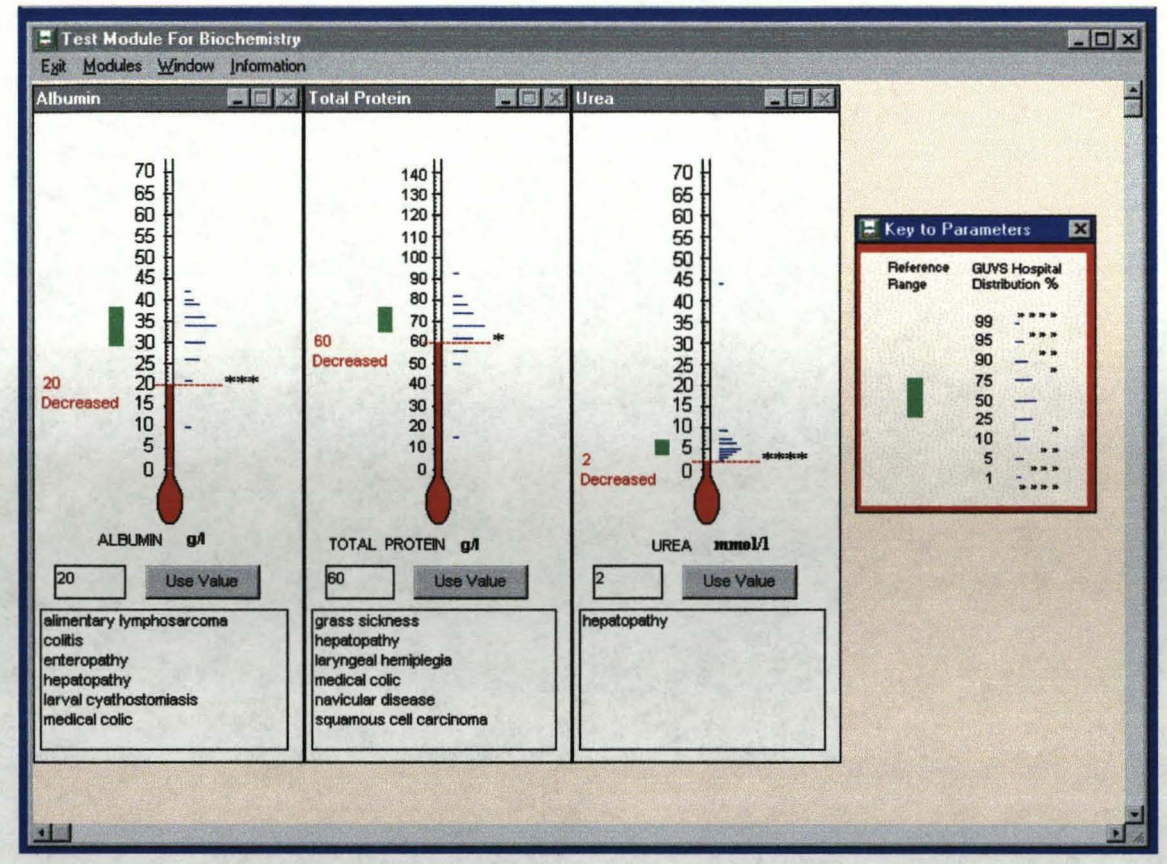


Figure 8-4 Sample screen from the Biochemical Thermometer which shows the thermometers for urea, albumin and total protein, with plasma concentrations for a new horse case of 2 mmol/l, 20 g/l and 60 g/l, respectively, having been entered to the system. The key on the right hand side of the screen explains the percentile starring system (see Figure 8-5). Also listed for each parameter are the most common diagnoses which were established in the interrogation of the GUVS equine population.

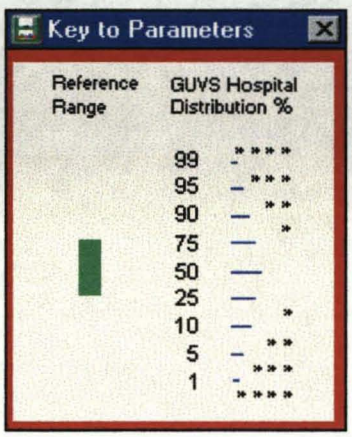


Figure 8-5 Key for the Biochemical Thermometer. The key details distribution of biochemistry results from the GUVS population based on percentile analysis, outlined in blue, and the depicts the GUVS parameter reference range in green.

The parameter concentration entered by the user was represented in a visual manner by the thermometer. Based on the percentile system as outlined in the key within Figure 8-5, the new value was compared to those previously obtained in horses at GUVS. A starring system first described by Little *et al.* (1994) was adopted to simplify the percentile concept further. In short, a value which lay in the top 1% of cases seen at GUVS was allocated four stars; a value which lay within the top 5% of cases was allocated three stars; a value which lay in the top 10% of cases was allocated two stars, and so on. Figure 8-4 indicates that the urea concentration of 2 mmol/l in a horse lay within the lowest 1% of values previously obtained, and was therefore allocated four stars. The results input for albumin and total protein may be similarly interpreted.

In addition, not only was the user made aware of how the values of the parameters measured compared to all of those previously seen at GUVS, a table of the most commonly occurring diagnoses corresponding to the percentile interval in which the specific value lay was then made available. It is important to note that the diagnoses displayed in Figure 8-4 were based on each individual parameter, and not on any combination of biochemistry parameters. However, it is interesting to observe that the diagnosis of hepatopathy appeared within the diagnosis box in Figure 8-4 in association with each of the concentrations entered for urea, albumin and total protein.

8.5 DISCUSSION

8.5.1 The Biochemical Thermometer

Through the interrogation of the GUVS hospital database, a novel personal computer-based decision support system for the objective interpretation of veterinary clinical biochemistry data was developed. The windows application was unique in design - based on a clinical thermometer analogy, and in development - based on clinical data from the hospital population. Through a user-friendly computer interface, clinicians were able to determine objectively whether a specific parameter value was abnormal, the degree of abnormality, and the most likely diagnoses from the GUVS hospital population with which it was associated.

Whilst this information is valuable, and certainly provides more guidance than a reference range approach, the potential for the system is greater.

8.5.2 Possibilities for future development

Importantly, the diagnoses listed in association with any parameter result represented the most common diagnoses which were established for all horses at GUVS previously observed with a biochemistry parameter value falling within a specific percentile band. The diagnosis list was therefore not fully comprehensive, and did not purport to include a list of all possible diagnoses which the clinician should consider. Future liaison with domain expert clinicians and clinical biochemists could yield the compilation of such comprehensive lists, thereby increasing the potential utilisation and value of the support system through implementation of heuristic algorithms (Reid *et al.*, 1996), in combination with the data driven model described.

Further work on the decision support system could then expand the system such that information on confirmatory tests, expected clinical signs and management of the diagnoses be obtainable via hypertext links to an extensive, regularly updated multimedia knowledgebase. This would improve the potential educational value of the product. Similar links could be established to a dynamic library containing information about established pathophysiological processes, and thereby promote true comprehension of parameter results. Finally, given that clinical biochemistry may be used not only as an aid to diagnosis, but also as an insight to the health status of an animal, a component of the support system which alerted the clinician to critical biochemical disturbances may be beneficial.

8.5.3 Decision support software and expert systems in veterinary medicine

In the past two or three decades, the use of computer technology within the medical domain has received increasing attention (Buffone and Moreau, 1995; Hopkins *et al.*, 1995; Miller, 1995). Esslemont *et al.* (1990) indicated that health management, knowledge-based expert or decision support systems were arising more quickly in animal health than they were in the medical field. Certainly, expert systems have been used for dairy herd management for a number of years (McKay *et al.*, 1988; Stowe, 1988a; Lissemore *et al.*, 1992a; Lissemore *et al.*, 1992b; Devir *et al.*, 1993). Diagnostic decision support systems, led initially by the introduction of "MYCIN" to the medical world in the early 1970's (Cecile *et al.*, 1990; Vos *et al.*, 1990; Chae *et al.*, 1992; Frost and Gillenson, 1993), have now begun to penetrate the veterinary market (White, 1988; McLeish and Cecile, 1990).

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In the area of animal health, programs were initially designed to facilitate ease of data recording, an example being "DAISY" - The Dairy Information System used in dairy herd management (Esslemont *et al.*, 1990). With the advent of micro-computers, dairy management software has continued to expand and develop (Dohoo, 1988; Esslemont *et al.*, 1990; Lissemore *et al.*, 1992b). Perhaps a combination of the increasingly data intensive nature of dairy farming (Smith, 1989; Spahr *et al.*, 1993; Pellerin *et al.*, 1994), coupled with the ability of domain experts to agree on elementary production rules, relating for example to milk production and calving index (Pellerin, 1994), hastened the development of expert systems in the agricultural area (Lissemore *et al.*, 1992b). Also, farming is a business which must be run in a cost-efficient manner, and provision of expert support may reduce economic loss (Collins and Morgan, 1991; Domecq *et al.*, 1991; Galligan *et al.*, 1991; Huirne *et al.*, 1991; Schmisseur and Gamroth, 1993; Williams and Esslemont, 1993). There now exists a wide range of data management and expert system software for use by the farmer in agriculture, from packages which focus on nutrition (Stowe, 1988a), to systems which diagnose reproductive problems, such as DairyFIX (McKay *et al.*, 1988), to automatic milking and feeding systems (Devir *et al.*, 1993).

Vos *et al.* (1990) highlighted that the use of expert systems in the veterinary field may be feasible, in the same manner as it was in medicine and agriculture. As early as 1988, Pollock and Fredericks (1988) suggested that the demand for increasingly sophisticated veterinary care was arising not only from the client, but also from veterinarians themselves. This, in conjunction with the growth of medical knowledge and the multi-factorial nature of decision making has resulted in the development of decision support systems for the veterinary domain.

The key elements of a useful and efficient computer-assisted medical diagnostic system include ease of use, justifiable diagnostic suggestions and case management recommendations with respect to diagnosis confirmation and possible therapy (Pollock, 1986; Pollock and Fredericks, 1988). One further feature which distinguishes computer-assisted information from that currently available through books and journals, is the ability for it to be readily updated. The introduction of diagnostic systems was not intended to replace the veterinarian (Fessler, 1984a; Stevens, 1986; Steward, 1995). Rather, their existence was to facilitate the veterinarian in ensuring appropriate patient care. Although veterinary computer-assisted diagnostic system technology remains

behind that of human medicine (Steward, 1995), a number of decision support systems are currently available in the veterinary field.

Maurice White, from the University of Cornell in the United States of America, was instrumental in the development of one of the earliest diagnostic support systems for use in the veterinary field - the CONSULTANT database (Fessler, 1984b; White, 1985; White and Lewkowicz, 1987; White, 1988). CONSULTANT is a large database containing a vast amount of regularly updated medical information on a number of domestic species. The computer-assisted diagnostic component of the database was created by a review of the veterinary literature. For each disease, a list of the species affected and expected clinical signs was recorded. A clinician examining a new case inputs the species and the clinical signs present, CONSULTANT then searches the database and compiles a list of those disease which match the input specifications. CONSULTANT continues to function as a veterinary diagnostic program, with information pertaining to in excess of 6000 diseases (http://netvet.wustl.edu/org/ aavi/vetcai.txt, 1996).

PROVIDES (Problem Oriented Veterinary Information and Decision Support) is a veterinary medical information system which originated in the 1980's (Pollock and Fredericks, 1988). However, in contrast to CONSULTANT, the diagnostic support component is, as suggested in the name, based on a problem oriented approach (Fessler, 1984b). Other diagnostic support systems include ASSOCIATE, a computer aided diagnostic medical reference system for dogs, cats, exotic and large animals; N-Squared computing, a diagnostic system for dogs, cats, birds, fish and nutrition; and BOVID, diagnostic software for the bovine (http://netvet.wustl.edu/org/ aavi/vetcai.txt).

More recently, software programmes intended to aid in the evaluation of diagnostic tests have been developed. Packages such as "TESTVIEW" (Gardner and Holmes, 1993) and "Testevaluation" (Gerhardt and Olsson, 1992) are designed for the evaluation of the clinical performance of quantitative diagnostic tests, and as such contain algorithms for the calculation of important test parameters such as sensitivity and specificity.

Of particular relevance to this discussion is the current availability of "HEMO" and "VetDiagnoster 1.0". HEMO was described in 1986 by Stevens as "a program designed to process a patient's database of laboratory test results and produce a report that provides a diagnostic analysis of these tests". The diagnostic interpretation offered

by HEMO is based on a reference range approach. Although this has a number of shortcomings, as detailed in 5.6.1, a weighted approach seeks to address these issues. Further assistance is offered in terms of a list of possible diagnoses that may account for the test abnormalities (Stevens, 1986). VetDiagnoster 1.0 was developed by M-R-Dx (Miller Research Diagnostics), founded in 1995. VetDiagnoster combines historical, clinical and laboratory observations to produce a report pertaining to the case under investigation (Miller, 1996).

8.5.4 Potential use of the Biochemical Thermometer

In contrast to the few diagnostic support systems currently available in the domain, the 'Biochemical Thermometer' is based on clinical data, not opinion. The system currently operates as a stand-alone package run on a personal computer. A further possible method of presenting the biochemistry diagnostic support could be through the integration of the support system to a species-specific expert system, such as that developed for the horse - EQWISE (Mellor *et al.*, 1994). Similarly, it is feasible that the biochemistry diagnostic support system could form an integral part of a commercial biochemistry analyser, adding to the potential utility of the analyser itself as well as more widely to continuing education in practice.

The results used for the development of the biochemistry decision support system were based on analysis undertaken at a certain point in time on biochemistry and diagnosis data maintained within the GUVS hospital database. A valuable extension to the system could involve networking the decision support system directly to the hospital database such that the diagnostic support offered by the system was re-established each time a new case entered the database. The system would therefore become a dynamic, self-updating diagnostic support tool, rather than a static description of the database. If appropriate practice-based biochemistry and diagnosis databases could be established, either on an individual level, or through networking of several practices, the system could equally be designed to function in the practice environment. This would be of immediate relevance in veterinary medicine, and have implications for the future application of information technology in the sphere of human medicine.

CHAPTER IX

GENERAL DISCUSSION AND CONCLUSIONS

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"Data become more useful when they are collated into carefully organised information, further collated, and then synthesised into knowledge."

D.L. White (1993)

9.1 OVERVIEW

The potential of a veterinary hospital database to yield important information was investigated. In 1988, the GUVS hospital database was updated and expanded to allow networked computerised recording of signalment, clinical, biochemical, haematological, microbiological and pathological information. Using the in-built query language, clinical biochemistry and corresponding diagnosis data were extracted from the database for analysis.

Initial investigation was undertaken for data relating to equine cases only. Using percentile analysis, clinical biochemistry results pertaining to 14 parameters were summarised. This simple non-parametric means of presenting the data provided an indication of how the biochemistry results obtained from the putatively unwell horses were spread. Graphical displays of the distribution of the results were also obtained, and indicated that none of the biochemistry parameters followed a normal distribution. Application of the percentile approach, which did not assume normality of the data, was therefore deemed appropriate for summarising and presenting the biochemistry data. Thereafter, rather than a parameter concentration being termed "within" or "outwith" the GUVS reference range, the concentration was classified as falling within one of ten percentile band intervals, namely the minimum and the 1^{st}, 2^{nd} and 5^{th}, 6^{th} and 10^{th}, and so on. This format for the classification of biochemistry data was superior to that of the reference interval because it indicated the degree of abnormality.

The second phase of the interrogation of GUVS database involved the use of the diagnosis data which corresponded to the biochemistry results. Within each of the percentile band intervals, the most common diagnoses were ascertained. Tabulation and

ranking of these diagnoses in order of frequency established differential diagnosis lists within each of the biochemistry parameter percentile band intervals. This method accentuated the differing patterns of diagnoses achieved with varying parameter concentrations.

Further to the realisation that the clinical biochemistry parameter concentration indeed affected the differential diagnosis, a means for quantifying the diagnostic power of the biochemistry test was sought. Using conditional probability and multiplicative probability rules, a Bayesian formula for the calculation of a likelihood ratio, termed the "Biochemical Factor" was developed. The Biochemical Factor indicated how many times more likely the diagnosis in question was, given the biochemistry parameter concentration, than before any biochemistry information was available. The Biochemical Factor was calculated for each of the most common diagnoses within each percentile band, for each biochemistry parameter.

Through a combination of the percentile and probabilistic approaches to the interpretation of the GUVS biochemistry data, a clinician could therefore establish whether a parameter concentration was abnormal, the degree of abnormality and the most likely associated diagnoses. Furthermore, the Biochemical Factor indicated how many times more likely a diagnosis was, given the parameter information. Thus, from one simple parameter concentration, important diagnostic information was established.

However, one of the issues associated with the analysis of the equine data was that the majority of the diagnoses used were clinical. Given that the diagnosis may have been made with the assistance of a panel of biochemistry results, quantification of the relationship between parameter concentration and diagnosis from within the database may have yielded biased results. This was unlikely to have affected the results to a great extent because it is unusual for a clinician to form a diagnostic opinion based solely on the results from one biochemistry parameter. Nevertheless, as a factor of the format for teaching of large animal medicine instituted at GUVS, an extensive database containing *post mortem* diagnoses for cattle cases was available. Interrogation of the biochemistry data and corresponding *post mortem* diagnosis data using the percentile analysis and Bayesian probabilistic approach was undertaken. The advantage of calculation of the Biochemical Factor based on *post mortem*, rather than clinical, diagnoses was that the *post mortem* diagnoses were made independently of the clinical biochemistry results.

Interpretation of clinical biochemistry parameters was further approached from the aspect of a disease profile. From the Biochemical Factor results obtained following interrogation of the cattle database, a visual representation of the results for a selection of diseases was compiled. Using different shades to represent the Biochemical Factor, a disease profile displaying Biochemical Factors relating to the ten percentile band intervals for thirteen biochemistry parameters was produced. A test dataset, randomly selected from the defined hospital cattle population, was employed for assessment of the disease profiles. Although each of the patterns compiled for the selected diseases differed, they were unreliable for the correct classification of a new test case.

The complex nature of the GUVS data under investigation, coupled with the small numbers for any one disease, limited the statistical procedures suitable for interpretation. However, a study was in progress to investigate the ability of clinical laboratory parameters to differentiate between cattle with acute and chronic inflammatory processes. The response variable consisted of only two groups, acute and chronic, and the smaller dataset was suitable for investigation using multiple logistic regression techniques. Following multivariable assessment, it was concluded that out of a total of twenty-nine laboratory parameters, the one which best differentiated between cattle with acute or chronic inflammatory processes was Serum Amyloid A, an acute phase protein. Thus, a single test may be capable of differentiating between cattle with acute or chronic inflammatory processes, having implications for both clinical care and meat hygiene.

Finally, following the recognition that valuable information may be retrieved from a hospital database, a decision support system which could convey the information to the clinician was developed. The computer-assisted diagnosis system focused on the development of an objective means for the interpretation of plasma biochemistry parameters, which had stemmed from the interrogation of the hospital database. Through a user-friendly interface, clinicians could determine whether a biochemistry value was abnormal, the degree of abnormality and the most likely associated diagnoses. The decision support system will be of use to undergraduate students, practising veterinarians and more widely in the veterinary domain.

9.2 RECOMMENDATIONS FOR THE GUVS HOSPITAL DATABASE

- Improvement of user interface for data input and extraction
- Implementation of database tutorials for staff
- Database projects for new clinical scholars
- Development of standard nomenclature
- Introduction of dedicated database manager position

Following investigation of data from within the GUVS hospital database, it was apparent that the system was not being utilised to an optimum level. Investigations for this thesis focused on clinical biochemistry data and diagnosis data. The clinical biochemistry database was complete, because it was either automatically uploaded to the database, or was manually updated on a daily basis. The necropsy database was mostly complete, because the pathologists used the database to compile their reports, and thereby effectively simultaneously updated the electronic database system. However, the database which posed most problems for this study was the clinical diagnosis database. Essentially, investigation of the canine and feline populations, using the percentile and probabilistic approaches described in this thesis for horses and cattle, was rendered impossible due to the sparse nature of the clinical diagnosis data. The responsibility for updating the clinical diagnosis component of the database lies with the clinician in charge of the case. Even after the recent upgrading of the hospital system which has markedly improved the time efficiency, the GUVS hospital database remains "unfriendly" to the user. This, in combination with the fact that many of the small animal clinicians do not appear to perceive the potential benefits of a comprehensive database system, perpetuates the non-entry of essential data to the computerised system.

Implementation of a number of simple recommendations may help encourage maintenance of a fully comprehensive GUVS hospital electronic database. The maxim "garbage in, garbage out" (Beard, 1992), highlights the requirement for improving ease of data entry to the GUVS hospital database. This could be established through the development of a windows-based, menu-driven user-interface for application on the existing networked PCs or for use within a more modern pen-based system (*2.4.1.2*). Similar alterations to facilitate data extraction would also be useful. To permit such

improvements, in particular the introduction of selection menus, a comprehensive coded nomenclature would have to be developed.

Kouri *et al.* (1994) suggested that if clinicians discover the benefits of accurate databases created by their own efforts, they will be motivated to improve the techniques of coding and storing case data. This leads to a final recommendation, which would be implementable immediately, and that is the promotion of tutorial sessions for new staff members, including clinical scholars, run jointly by the database manager and an existing member of clinical staff familiar with the system. Such tutorials may not only encourage data entry, but may be used to emphasise the value of maintaining a comprehensive system. Furthermore, perhaps implementing small projects for new clinical scholars, on an appropriate topic of their choice, which would necessitate their working with the database, may serve not only familiarise them with the capabilities of the system, but may also lead to increasing knowledge of disease and therefore to possible journal publications. Implementation and upholding of these recommendations would require greater commitment from staff and contributors, and more rigorous management of the hospital database.

9.3 DATA OWNERSHIP

Maintenance of an accurate and fully comprehensive database system requires much effort from all personnel involved. In the present climate, as the potential utility of raw data is being realised, political issues pertaining to data ownership may impair possible epidemiological investigations. Within a computerised veterinary medical record system, a number of persons may claim data ownership. These include the owner of the animal patient; persons responsible for generation of the data, such as biochemistry laboratory technicians or diagnosticians; those responsible for data input to the electronic system; personnel involved in the development and maintenance of the database; and the institute itself.

If each of these groups were to lay claim to the data, then investigations such as detailed within this thesis would be impossible. The issue of data ownership is thus one which must be addressed, clarified and controlled at the highest level so that epidemiological research may be optimised. This should ensure that the potential to derive useful information from raw data be granted, ultimately promoting further contribution to veterinary medicine as a whole.

9.4 THE STUDY OF A POPULATION

This thesis has outlined the investigation of a referral hospital population. One of the strengths of the investigation was that the number of cases involved allowed quantification of *a priori* and *a posteriori* probabilities for different diagnoses in association with differing plasma biochemistry parameter concentrations. These probabilistic quantities have been more often described in the literature as "common", or "rare" (Long *et al.*, 1992; Korver and Lucas, 1993), if assessed at all. Lord Kelvin (1824-1907) stated, "I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind." This early observation encourages the continuing quest for comprehension and quantification of the world around us. The study of disease in populations, termed "epidemiology" has received increasing interest in the veterinary domain. For many, the emphasis of veterinary medicine has been on the assessment and treatment of individual animals. However, induced initially by the requirement to instigate control measures for large scale outbreaks of infectious disease, such as equine influenza in England in 1688 (Thrusfield, 1995), preventive population medicine has developed and advanced. Following the Second World War, 1939-1945, the focus of epidemiological studies was expanded to include the study of chronic or rare conditions (Davies, 1983). While Doll in 1959 famously identified an association in humans between smoking and lung cancer, the appreciation of the potential of epidemiological studies within the veterinary environment was expressed by Cohen *et al.* (1959). However, McDermott (1995) suggests that it is only in the last 30 years that quantitative methods have been used widely in veterinary epidemiology. This may be as a result of the technological revolution allowing computerised recording and retrieval of large datasets, suitable for quantitative analysis. In 1988, a survey of epidemiological study designs appearing in a practice journal was conducted (Smith, 1988), and noted that more than 90% of case reports included fewer than five cases. Powell (1989) and Ribble *et al.* (1989) suggested that establishing computerised record-keeping systems in practices would have significant implications for obtaining information about the practice population.

Certainly, in recent years, the use of hospital populations for investigation of disease has become evident in the medical domain. For example, Kouri *et al.* (1994) highlighted the usefulness of the establishment of reference values based on data from both control and diseased populations, made possible by the introduction of automation and computerisation. Similarly, Zwetsloot-Schonk (1990) suggested the importance of using data from clinical practice populations, with hospital information systems facilitating the investigation of such populations. In veterinary medicine, emerging use of hospital databases for epidemiological studies is also apparent (Morton, 1996). With such increasing use of hospital databases in veterinary research, the requirement for assured reliability of the electronic data is of increasing importance. Pollari *et al.* (1996) conducted one of the first evaluations of the quality of data maintained within a computerised hospital database system, that of the Veterinary Teaching Hospital, Ontario Veterinary College. Information from the paper medical record was compared to that which had been entered to the computerised medical record by health record technicians. The conclusion was that the accuracy of information in the database was inadequate for the intended research subject. The publication of further such evaluations perhaps will serve to encourage careful maintenance of the electronic medical record by all personnel involved, thereby promoting the potential for future epidemiological investigations.

9.5 IMPLICATIONS OF COMPUTER TECHNOLOGY IN THE VETERINARY DOMAIN

In the fields of both human and veterinary medicine, it is hoped that the technological revolution will help doctors and veterinarians realise their maximum potential with respect to individual patient care as well as to prevention and treatment of disease within populations (Thrusfield, 1983a; Buffone and Moreau, 1995; Netzer *et al.*, 1996). Computer technology has entered the consulting room not only through automation of technical laboratory analysers, but also through the continued development of the electronic medical record and database systems, computer-assisted decision support systems and, most recently, through the Internet.

Smith (1986) suggested that the ability of veterinary medicine to evolve would not depend simply on the rate of development of computer technology, but also on the ability of the profession to accept the new philosophy. However, as has been evidenced by the rapid and continued growth of the Internet, or the "information super-highway"

(Fine *et al.*, 1995; Hopkins *et al.*, 1995) and, in particular, the success of electronic mailing lists, such as VETPLUS-L (VETPLUS-L, 1998) and VETMED-L, which serve to allow veterinarians to communicate with others anywhere in the world, the veterinary profession appears willing to consider computer technology (BSAVA News, 1997). Availability of a number of high-impact medical journals, such as the British Medical Journal (British Medical Journal, 1998), as well as commercially maintained literature databases, such as the Bath Information and Data Services (BIDS, 1998) and Medline (Medline, 1998), in electronic format on the Internet may also promote acceptance of new technology.

As knowledge of disease in the veterinary domain continues to grow, it is vital that all members of the profession remain current. In Section 2.90 of the Royal College of Veterinary Surgeons (RCVS) Guide to Professional Conduct, 1996, it states, "It is important for veterinarians to keep up to date with general developments in veterinary science, especially in the sectors in which they are practising". Recently, the RCVS has recommended that veterinarians complete 35 hours of continuing professional development (CPD) each year (O'Malley, 1997). Such indications from the professional body serve to encourage members in their quest to function at an optimum level. Although the RCVS has yet to deliver detailed guidelines as to how the CPD will be assessed, it may be that in future, interactive multi-media teaching, such as that described by Whithear *et al.* (1994) and Hooper *et al.* (1995), and assessment systems will become available, either on CD-ROM or over the Internet.

Almost certain, is the continued application of computer technology to the field of veterinary medicine. As improvements in computerised medical recording systems promote the further development and validation of computer-assisted decision support software, clinical judgement will be enhanced. Time magazine (Gorman, 1995) recently reported that 80000 patients per year may die in American human hospitals through misdiagnosis and inappropriate treatment. Such statistics highlight the need for accessible decision support. In the future, referral to computer-assisted diagnostic support systems may be mandatory.

9.6 THE FUTURE

One of the key aspects discussed within this thesis was the application of Bayesian theory to the interpretation of clinical biochemistry data. The odds-likelihood ratio form of the

theory, discussed fully in Chapters 4 and 5, was found to be valuable for biochemistry and diagnostic decision support in this thesis. Notably, this form of the equation is gaining in popularity in human medicine (Henderson, 1993; Miettinen and Caro, 1994). However, although the investigation of plasma biochemistry parameters on an individual level within this thesis was valuable, it is more usual for a clinician to utilise more than one paraclinical test, in conjunction with the historical and clinical information, to obtain a clinical diagnosis (Martin and Bonnett, 1987). Therefore, identification of appropriate means for the expansion of the study to investigate several clinical biochemistry parameters simultaneously would be beneficial. A key recognition in the pursuit of an appropriate method for the interpretation of a combination of biochemistry parameters, is that the parameters are not independent (Kerr, 1989; Dart *et al.*, 1992; Jacobs *et al.*, 1992).

One possibility would be the development of a Bayesian Belief Network, which permits the combination of diagnostic evidence in a cumulative manner (Hamilton *et al.* 1994). Bayesian belief networks have been used in medicine, for example, to assist in the diagnosis of fine needle aspiration biopsy specimens of the breast (Hamilton *et al.* 1994), and several medical papers discuss their development in specific situations (Korver and Lucas, 1993; Chevrolat *et al.*, 1994; Montironi *et al.*, 1996). Furthermore, Bill Gates, Chairman of Microsoft, the world's largest computer software company, has promoted the role of Bayesian systems in the future of computer technology (Helm, 1996), which suggests that Bayesian Belief Networks should indeed be investigated with respect to the GUVS biochemistry and diagnosis data.

However, even before statistical interpretation of parameter combinations is performed, the Biochemical Thermometer, the biochemistry decision support system which was derived from the investigation of the hospital database, may be of importance in the veterinary domain. Shimizu *et al.* (1990) and Hoeke *et al.* (1991) have highlighted the advantages of visual or graphical presentation of laboratory data in the medical domain. Through a simple thermometer analogy, a visual representation of a patient's metabolic state is achieved using the Biochemical Thermometer. Furthermore, it assists with the diagnostic process, and therefore helps ensure appropriate therapy and management of a case is instituted (Martin and Bonnett, 1987; Todd *et al.*, 1993).

It is important to appreciate that the results presented in this thesis were based on the GUVS referral population. Given that the probabilistic measures are population

specific (Korver and Lucas, 1993; Miettinen and Caro, 1994), the results are only applicable within the hospital population. However, as suggested in Chapter 5, with increasing automation and computerisation in the veterinary field (Stowe, 1988b), development of a practice-based database of biochemistry results may be feasible in the near future. Such a database could be established within an individual practice, or could be maintained over a number of networked practice databases (Stone and Thrusfield, 1989), perhaps even on a National level. Institution of the percentile system within each practice or laboratory would allow standardisation and thus amalgamation of all the biochemistry results. If an independent gold standard for defining diagnosis (Henderson, 1993) with an associated accepted diagnosis nomenclature could be established, the Biochemical Factor could similarly be implemented within the practice-based population.

In conclusion, this study has realised the ability to convert raw data into useful knowledge. Through the interrogation of a hospital database, a method for the objective interpretation of clinical biochemistry data has been revealed. The novel approaches and techniques described offer a realistic solution to the issue of clinical biochemistry interpretation in the veterinary domain. Extension of the study towards the development of an automatically updated, dynamic, practice-based biochemistry and diagnosis database would have important implications for the future of biochemistry interpretation in the veterinary domain.

APPENDIX I

EQUINE BIOCHEMISTRY DESCRIPTIVE STATISTICS

Statistic	Biochemistry Parameter		
	AP (U/l)	Creatinine (µmol/l)	Total protein (g/l)
Mean	466.7	146.7	67.5
Standard Error	21.3	8.7	0.4
Median	343.5	123	67
Mode	310	112	66
Standard Deviation	519.3	209.9	10.1
Kurtosis	51.76	223.82	6.20
Skewness	6.05	13.59	-0.44
Range	6699	4036	115
Minimum	1	14	15
Maximum	6700	4050	130

Table I-1 Descriptive statistics for plasma alkaline phosphatase (AP), creatinine and total protein results from equine referral cases seen at GUVS over study period.

Statistic	Biochemistry Parameter		
	Globulin (g/l)	AST (U/l)	Sodium (mmol/l)
Mean	34.7	350.1	136.3
Standard Error	0.4	10.9	0.2
Median	33	292	137
Mode	31	319	136
Standard Deviation	9.5	261.4	4.7
Kurtosis	12.16	57.59	8.98
Skewness	2.03	5.96	-1.36
Range	107	3729	55
Minimum	10	11	104
Maximum	117	3740	159

Table I-2 Descriptive statistics for plasma globulin, aspartate amino-transferase (AST) and sodium results from equine referral cases seen at GUVS over study period.

Statistic	Biochemistry Parameter		
	Chloride (mmol/l)	Potassium (mmol/l)	Bilirubin (µmol/l)
Mean	97.9	3.62	32.0
Standard Error	0.25	0.03	0.9
Median	98	3.6	26
Mode	98	3.6	27
Standard Deviation	6.0	0.83	22.2
Kurtosis	11.54	10.70	4.48
Skewness	-1.39	1.87	1.80
Range	75	9.2	168
Minimum	49	1.3	1
Maximum	124	10.5	169

Table I-3 Descriptive statistics for plasma chloride, potassium and bilirubin results from equine referral cases seen at GUVS over study period.

Statistic	Biochemistry Parameter		
	Calcium (mmol/l)	Phosphate (mmol/l)	Magnesium (mmol/l)
Mean	2.912	1.108	0.663
Standard Error	0.013	0.022	0.009
Median	2.95	1.00	0.66
Mode	2.95	0.96	0.66
Standard Deviation	0.288	0.511	0.194
Kurtosis	10.81	11.20	93.49
Skewness	-2.23	2.48	7.84
Range	2.98	4.48	2.92
Minimum	0.59	0.27	0.25
Maximum	3.57	4.75	3.17

Table I-4 Descriptive statistics for plasma calcium, phosphate and magnesium results from equine referral cases seen at GUVS over study period.

APPENDIX II

EQUINE BIOCHEMICAL FACTOR RESULTS

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Surgical colic	6.8
2 - 5	Medical colic	3.0
	Surgical colic	3.4
6 - 10	Medical colic	2.1
11 - 25	Medical colic	1.3
	Laryngeal hemiplegia	2.2
	Sarcoids	1.1
	Cardiological problem	2.0
	COPD*	1.0
	Navicular disease	1.4
26 - 50	Sarcoids	1.4
	Medical colic	1.0
	COPD	1.4
	Navicular disease	1.7
	Laminitis	1.1
51 - 75	COPD	1.6
	Cushing's disease	2.0
	Laminitis	1.8
	Sarcoids	1.4
	Grass sickness	2.0
76 - 90	Cryptorchid	3.7
	Hepatopathy	2.5
	Medical colic	1.1
	Cardiological problem	2.8
	Cushing's disease	1.7
	Sarcoids	1.1
91 - 95	Hepatopathy	3.6
	Laminitis	3.2
	Medical colic	1.2
	Surgical colic	2.4
	Grass sickness	2.6
	Alimentary lymphosarcoma	7.9
	Larval cyathostomiasis	7.9
96 - 99	Hepatopathy	8.6
	Hyperlipaemia	11.6
	Surgical colic	3.1
99 - max.	Hyperlipaemia	93.0

*Chronic obstructive pulmonary disease

Table II-1 Biochemical Factor calculated for the most common diagnoses, within each percentile band for alkaline phosphatase results from GUVS equine referral cases.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Surgical colic	12.7
	Hepatopathy	15.3
2 - 5	Laminitis	10.0
	Hepatopathy	5.0
	Chronic enteropathy	10.1
	Medical colic	1.5
6 - 10	Cushing's disease	5.4
	Hepatopathy	4.7
	Medical colic	1.6
11 - 25	Cushing's disease	4.8
	Cryptorchid	1.7
	Tooth root abscess	2.7
	Grass sickness	1.5
	Navicular disease	1.3
26 - 50	Sarcoids	1.5
	Navicular disease	1.9
	COPD*	1.2
	Cryptorchid	1.2
	Medical colic	0.5
	Surgical colic	0.8
51 - 75	Medical colic	1.6
	COPD	1.7
	Sarcoids	1.4
	Laminitis	1.3
	Cardiological problem	2.0
	Laryngeal hemiplegia	1.6
76 - 90	Surgical colic	1.9
	Medical colic	0.9
	Cardiological problem	2.3
	EIPH†	5.7
	Laryngeal hemiplegia	1.9
	Sarcoids	1.0
91 - 95	Medical colic	4.3
	Cryptorchid	2.0
	Surgical colic	2.3
96 - 99	Grass sickness	12.0
	Colitis	10.0
	Medical colic	1.7
	Surgical colic	2.9
99 - max.	Nephropathy	36.5

*Chronic obstructive pulmonary disease; †Exercise induced pulmonary haemorrhage

Table II-2 Biochemical Factor calculated for the most common diagnoses, within each percentile band for creatinine results from GUVS equine referral cases.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Medical colic	6.3
2 - 5	Colitis	13.2
	Chronic enteropathy	9.6
	Medical colic	1.5
	Alimentary lymphosarcoma	9.7
6 - 10	Angular limb deformity	7.4
	Chronic enteropathy	24.3
11 - 25	Angular limb deformity	3.5
	Cryptorchid	2.1
	Medical colic	0.8
	Grass sickness	1.3
	Hepatopathy	1.3
	Laryngeal hemiplegia	1.6
	Navicular disease	1.3
	Squamous cell carcinoma	2.6
26 - 50	Cryptorchid	2.3
	Surgical colic	1.8
	COPD*	1.3
	Sarcoids	1.2
	Laryngeal hemiplegia	1.8
	Cushing's disease	1.2
51 - 75	Medical colic	1.4
	Sarcoids	1.7
	COPD	1.3
	Laminitis	1.6
	Cushing's disease	1.4
76 - 90	Grass sickness	2.5
	Laminitis	2.2
	Hyperlipaemia	4.3
	Laminitis	1.7
	Navicular disease	2.1
91 - 95	Sarcoids	3.8
	Medical colic	1.8
	Grass sickness	3.9
96 - 99	Hepatopathy	9.8
	Cushing's disease	3.3
	Grass sickness	3.6
99 - max.	Medical colic	7.6

*Chronic obstructive pulmonary disease

Table II-3 Biochemical Factor calculated for the most common diagnoses, within each percentile band for total protein results from GUVS equine referral cases.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Medical colic	3.3
2 - 5	Angular limb deformity	7.1
	Colitis	4.3
	Chronic enteropathy	4.9
6 - 10	Medical colic	1.4
	Sarcoids	1.9
11 - 25	Cryptorchid	2.4
	Medical colic	1.1
	Laryngeal hemiplegia	2.7
	Surgical colic	1.4
	Navicular disease	1.6
26 - 50	Cryptorchid	1.6
	Medical colic	1.2
	COPD*	1.2
	Cushing's disease	1.6
	Sarcoids	1.2
	Surgical colic	1.3
51 - 75	Laminitis	2.2
	Sarcoids	1.7
	COPD	1.2
	Grass sickness	1.7
	Navicular disease	1.7
76 - 90	Medical colic	1.0
	Grass sickness	2.1
	Tooth root abscess	2.8
91 - 95	COPD	3.4
	Hepatopathy	4.6
96 - 99	Hepatopathy	7.1
	Medical colic	2.7
	Cushing's disease	4.9
	Sarcoids	2.1
	Tooth root abscess	4.7
99 - max.	Hepatopathy	6.6

*Chronic obstructive pulmonary disease

Table II-4 Biochemical Factor calculated for the most common diagnoses, within each percentile band for globulin results from GUVS equine referral cases.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Grass sickness	8.1
2 - 5	Medical colic	3.0
6 - 10	Surgical colic	2.4
	Sarcoids	1.6
11 - 25	Medical colic	1.1
	Navicular disease	2.0
	Sarcoids	1.1
	Cushing's disease	1.3
	Grass sickness	1.6
26 - 50	Angular limb deformity	2.7
	Cushing's disease	1.2
	Sarcoids	0.8
	Colitis	2.3
	COPD*	0.9
	Laryngeal hemiplegia	1.3
	Navicular disease	1.2
	Tooth root abscess	1.3
51 - 75	Medical colic	1.6
	Cryptorchid	1.7
	Sarcoids	1.5
	COPD	1.5
	Laryngeal hemiplegia	1.9
	Laminitis	1.1
76 - 90	Cryptorchid	2.5
	Surgical colic	2.6
	Laminitis	2.4
	Medical colic	1.4
	COPD	1.9
	Sarcoids	1.1
91 - 95	Surgical colic	3.7
	Cushing's disease	3.7
	Laminitis	3.5
	Choke	10.0
	Grass sickness	3.0
96 - 99	Hepatopathy	14.8
	Surgical colic	5.3
	Laminitis	3.1
99 - max.	Laminitis	5.0

*Chronic obstructive pulmonary disease

Table II-5 Biochemical Factor calculated for the most common diagnoses, within each percentile band for aspartate amino-transferase results from GUVS equine referral cases.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Chronic enteropathy	18.0
2 - 5	Chronic enteropathy	12.0
	Medical colic	1.8
	Hepatopathy	3.9
	Colitis	5.7
	Hyperlipaemia	7.9
	Laminitis	2.2
	Larval cyathostomiasis	9.8
6 - 10	Medical colic	2.8
	Surgical colic	3.4
	Grass sickness	5.2
	Alimentary lymphosarcoma	13.6
11 - 25	Medical colic	1.6
	Cushing's disease	1.7
	Hepatopathy	1.7
	Laminitis	1.5
	Cryptorchid	1.2
	Sarcoids	1.0
26 - 50	Medical colic	1.5
	COPD*	1.8
	Cryptorchid	1.4
	Sarcoids	1.3
	Cushing's disease	1.3
	Navicular disease	1.1
	Tooth root abscess	1.4
51 - 75	Surgical colic	1.7
	Sarcoids	1.2
	Cryptorchid	1.4
	COPD	1.1
	Laryngeal hemiplegia	1.9
76 - 90	Cardiological problem	3.4
	Surgical colic	1.6
	Squamous cell carcinoma	4.5
91 - 95	Medical colic	1.3
	Ethmoid haematoma	21.0
	Laryngeal hemiplegia	3.2
	Sarcoids	1.9
96 - 99	Colitis	9.8
	Navicular disease	4.1
99 - max.	Medical colic	6.7
	Grass sickness	9.6

*Chronic obstructive pulmonary disease

Table II-6 Biochemical Factor calculated for the most common diagnoses, within each percentile band for sodium results from GUVS equine referral cases.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Cushing's disease	14.5
2 - 5	Choke	11.6
	Colitis	8.4
	Lymphosarcoma	11.6
6 - 10	COPD*	2.7
	Medical colic	1.3
	Chronic enteropathy	7.2
	Hepatopathy	2.8
	Grass sickness	2.1
11 - 25	Cryptorchid	2.7
	Medical colic	1.2
	Surgical colic	2.1
	Hepatopathy	1.8
	Cardiological problem	2.3
	Laminitis	1.6
26 - 50	Medical colic	1.8
	Surgical colic	1.6
	COPD	1.1
	Grass sickness	1.9
	Laminitis	1.6
	Sarcoids	1.1
51 - 75	Sarcoids	1.8
	COPD	1.4
	Cryptorchid	1.3
	Medical colic	0.4
	Hepatopathy	0.8
	Navicular disease	0.8
76 - 90	Navicular disease	2.5
	Cardiological problem	1.9
	Surgical colic	1.0
	COPD	0.9
	Laryngeal hemiplegia	1.6
	Lymphosarcoma	3.9
	Tooth root abscess	1.6
91 - 95	Medical colic	2.3
	Grass sickness	5.8
	Narcolepsy	16.3
96 - 99	Cushing's disease	4.0
	Laminitis	4.0
99 - max.	Ruptured bladder	42.2

*Chronic obstructive pulmonary disease

Table II-7 Biochemical Factor calculated for the most common diagnoses, within each percentile band for potassium results from GUVS equine referral cases.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Chronic enteropathy	10.4
2 - 5	Surgical colic	5.8
	Chronic enteropathy	5.3
	Choke	10.5
	Hepatopathy	3.4
6 - 10	Medical colic	2.1
	Cardiological problem	5.0
	Hyperlipaemia	10.1
11 - 25	Medical colic	1.3
	Cushing's disease	2.7
	Sarcoids	1.6
	Cryptorchid	1.7
	Hepatopathy	1.7
26 - 50	Medical colic	1.2
	Cryptorchid	1.2
	Sarcoids	1.5
	Cardiological problem	2.8
	COPD*	0.8
	Cushing's disease	1.1
	Grass sickness	1.3
51 - 75	Medical colic	1.1
	Laminitis	1.8
	COPD	1.3
	Laryngeal hemiplegia	2.2
	Surgical colic	1.1
	Sarcoids	0.9
76 - 90	Navicular disease	2.8
	Cryptorchid	1.0
	Tooth root abscess	2.2
	Medical colic	0.5
	Colitis	2.5
	COPD	0.8
	Cushing's disease	1.1
91 - 95	COPD	2.9
	Hepatopathy	2.6
	Navicular disease	2.6
96 - 99	Surgical colic	6.5
99 - max.	Grass sickness	18.2

*Chronic obstructive pulmonary disease

Table II-8 Biochemical Factor calculated for the most common diagnoses, within each percentile band for chloride results from GUVS equine referral cases.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Grass sickness	9.0
2 - 5	Cryptorchid	2.5
	Medical colic	1.9
6 - 10	Cryptorchid	4.9
	Colitis	4.4
	Narcolepsy	13.5
11 - 25	Sarcoids	1.5
	Tooth root abscess	2.9
	Cryptorchid	1.2
	Cushing's disease	1.9
	Laminitis	1.7
26 - 50	COPD*	1.3
	Cardiological problem	2.4
	Cryptorchid	0.9
	Medical colic	0.6
	Cushing's disease	1.4
	Sarcoids	0.9
51 - 75	Medical colic	1.0
	Sarcoids	1.2
	COPD	1.2
	Navicular disease	1.5
	Laminitis	1.0
	Laryngeal hemiplegia	1.6
76 - 90	Surgical colic	2.9
	Navicular disease	2.5
	Cryptorchid	0.9
	Medical colic	0.7
	Hepatopathy	1.5
	Sarcoids	0.9
91 - 95	Medical colic	4.3
	Grass sickness	9.5
	Surgical colic	4.4
	COPD	2.2
96 - 99	Grass sickness	12.1
	Medical colic	3.9
	Surgical colic	7.5
99 - max.	Choke	75.4

*Chronic obstructive pulmonary disease

Table II-9 Biochemical Factor calculated for the most common diagnoses, within each percentile band for bilirubin results from GUVS equine referral cases.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Chronic enteropathy	10.0
2 - 5	Surgical colic	4.7
	Colitis	9.1
	Medical colic	1.6
6 - 10	Grass sickness	7.1
	Medical colic	1.9
	Surgical colic	2.2
	Hepatopathy	2.6
11 - 25	Surgical colic	2.7
	Medical colic	1.3
	Cryptorchid	1.3
	Cardiological colic	2.0
	COPD*	0.9
	Cushing's disease	1.3
	Grass sickness	1.7
26 - 50	Medical colic	1.3
	Laminitis	2.0
	Sarcoids	1.3
	Cryptorchid	1.1
	Grass sickness	1.8
	Navicular disease	1.3
51 - 75	Medical colic	1.2
	COPD	1.2
	Laryngeal hemiplegia	2.6
	Sarcoids	1.1
	Tooth root abscess	2.6
76 - 90	Sarcoids	2.2
	COPD	1.7
	Cushing's disease	1.7
	Hepatopathy	1.4
	Navicular disease	1.3
91 - 95	Arthritis	4.4
96 - 99	Cryptorchid	4.4
	Cushing's disease	3.6
99 - max.	Medical colic	3.0

*Chronic obstructive pulmonary disease

Table II-10 Biochemical Factor calculated for the most common diagnoses, within each percentile band for calcium results from GUVS equine referral cases.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Chronic enteropathy	10.0
2 - 5	Surgical colic	4.7
	Colitis	9.1
	Medical colic	1.6
6 - 10	Grass sickness	7.1
	Medical colic	1.9
	Surgical colic	2.2
	Hepatopathy	2.6
11 - 25	Surgical colic	2.7
	Medical colic	1.3
	Cryptorchid	1.3
	Cardiological colic	2.0
	COPD*	0.9
	Cushing's disease	1.3
	Grass sickness	1.7
26 - 50	Medical colic	1.3
	Laminitis	2.0
	Sarcoids	1.3
	Cryptorchid	1.1
	Grass sickness	1.8
	Navicular disease	1.3
51 - 75	Medical colic	1.2
	COPD	1.2
	Laryngeal hemiplegia	2.6
	Sarcoids	1.1
	Tooth root abscess	2.6
76 - 90	Sarcoids	2.2
	COPD	1.7
	Cushing's disease	1.7
	Hepatopathy	1.4
	Navicular disease	1.3
91 - 95	Arthritis	4.4
96 - 99	Cryptorchid	4.4
	Cushing's disease	3.6
99 - max.	Medical colic	3.0

*Chronic obstructive pulmonary disease

Table II-10 Biochemical Factor calculated for the most common diagnoses, within each percentile band for calcium results from GUVS equine referral cases.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Surgical colic	11.3
2 - 5	Sarcoids	4.0
	Medical colic	1.9
6 - 10	Tooth root abscess	3.1
11 - 25	Medical colic	1.8
	Cushing's disease	2.9
	Navicular disease	2.2
	Colitis	3.0
	Hepatopathy	2.0
26 - 50	Cushing's disease	2.0
	Medical colic	0.9
	COPD*	1.2
	Laminitis	1.3
	Laryngeal hemiplegia	1.9
51 - 75	Medical colic	1.1
	Laminitis	1.6
	Sarcoids	1.4
	Surgical colic	1.3
	COPD	1.1
	Cryptorchid	0.9
76 - 90	Cryptorchid	2.6
	Sarcoids	1.8
	Laminitis	1.6
	Medical colic	0.8
	Surgical colic	1.5
	Tooth root abscess	1.8
91 - 95	Cryptorchid	5.7
	Medical colic	1.4
	Ruptured bladder	20.1
96 - 99	Angular limb deformity	14.1
99 - max.	Grass sickness	14.0

*Chronic obstructive pulmonary disease

Table II-11 Biochemical Factor calculated for the most common diagnoses, within each percentile band for phosphate results from GUVS equine referral cases.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Colitis	32.0
2 - 5	Medical colic	3.9
	Surgical colic	6.6
	Hepatopathy	4.3
	Hyperlipaemia	12.5
	Laminitis	2.8
6 - 10	Medical colic	3.1
	Choke	10.2
	Surgical colic	2.5
	Hepatopathy	3.5
	Laminitis	2.2
11 - 25	Medical colic	1.3
	Sarcoids	1.6
	Surgical colic	1.5
	Cryptorchid	1.3
	Cushing's disease	1.8
26 - 50	Cryptorchid	1.8
	Medical colic	1.3
	COPD*	1.4
	Sarcoids	1.0
51 - 75	COPD	2.1
	Laminitis	1.2
	Laryngeal hemiplegia	2.0
	Sarcoids	1.0
	Cryptorchid	0.8
	Tooth root abscess	1.6
76 - 90	Navicular disease	2.8
	Laryngeal hemiplegia	2.2
	Medical colic	0.6
	Surgical colic	1.0
	COPD	1.0
	Hepatopathy	1.4
	Sarcoids	0.7
	Wasting	3.2
91 - 95	Laminitis	4.3
	Myopathy	12.0
	Navicular disease	3.1
	Tooth root abscess	4.3
96 - 99	Grass sickness	6.5
99 - max.	Medical colic	7.7

*Chronic obstructive pulmonary disease

Table II-12 Biochemical Factor calculated for the most common diagnoses, within each percentile band for magnesium results from GUVS equine referral cases.

APPENDIX III

BOVINE BIOCHEMISTRY DESCRIPTIVE STATISTICS

Statistic	Biochemistry Parameter		
	Total protein (g/l)	Albumin (g/l)	Globulin (g/l)
Mean	78.5	28.4	50.0
Standard Error	0.6	0.2	0.6
Median	78	28	48
Mode	80	27	39
Standard Deviation	15.5	6.4	16.4
Kurtosis	0.82	1.65	0.00
Skewness	0.11	0.30	0.53
Range	121	58	99
Minimum	4	2	2
Maximum	125	60	101

Table III-1 Descriptive statistics for plasma total protein, albumin and globulin results from bovine referral cases seen at GUVS over study period.

Statistic	Biochemistry Parameter		
	Potassium (mmol/l)	Chloride (mmol/l)	AP (U/l)
Mean	4.31	94.5	204.8
Standard Error	0.05	0.3	5.9
Median	4.2	96	154
Mode	4.4	98	107
Standard Deviation	1.29	9.2	159.9
Kurtosis	65.11	4.09	10.55
Skewness	5.05	-1.28	2.58
Range	22	77	1425
Minimum	1	49	30
Maximum	23	126	1455

Table III-2 Descriptive statistics for plasma potassium, chloride and alkaline phosphatase (AP) results from bovine referral cases seen at GUVS over study period.

Statistic	Biochemistry Parameter		
	Calcium (mmol/l)	Magnesium (mmol/l)	Phosphate (mmol/l)
Mean	2.333	0.675	2.137
Standard Error	0.009	0.009	0.031
Median	2.35	0.65	2.04
Mode	2.37	0.52	2.03
Standard Deviation	0.247	0.230	0.811
Kurtosis	2.13	12.15	9.09
Skewness	-0.50	2.45	2.17
Range	2.14	2.36	7.13
Minimum	1.2	0.14	0.25
Maximum	3.34	2.5	7.38

Table III-3 Descriptive statistics for plasma calcium, magnesium and phosphate results from bovine referral cases seen at GUVS over study period.

Statistic	Biochemistry Parameter		
	AST (U/l)	Bilirubin (µmol/l)	Creatinine (µmol/l)
Mean	134.0	6.0	152.7
Standard Error	6.3	0.3	12.2
Median	87	2	105
Mode	71	1	90
Standard Deviation	164.4	8.8	300.8
Kurtosis	58.26	17.64	275.80
Skewness	6.17	3.37	14.80
Range	2290	86	6152
Minimum	8	0	43
Maximum	2298	86	6195

Table III-4 Descriptive statistics for plasma aspartate amino-transferase (AST), bilirubin and creatinine results from bovine referral cases seen at GUVS over study period.

APPENDIX IV

BOVINE BIOCHEMICAL FACTOR RESULTS

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Johne's disease	4.8
2 - 5	Johne's disease	9.8
	Mucosal disease	1.5
6 - 10	Congenital cardiac defect	2.9
	CSPD*	0.6
	Enteropathy-chronic lymphocytic	7.9
	Johne's disease	0.9
	Lymphosarcoma	1.1
	Mucosal disease	0.6
	Ostertagiasis	3.5
	Ulceration abomasal	3.1
11 - 25	Johne's disease	2.7
	Mucosal disease	1.3
	CSPD	0.9
	Ostertagiasis	3.0
	Ulceration abomasal	2.7
26 - 50	Mucosal disease	1.2
	CSPD	0.9
	Congenital cardiac defect	1.8
	Lymphosarcoma	1.0
	Pericarditis traumatic	1.2
51 - 75	CSPD	1.6
	Mucosal disease	0.8
	Lymphosarcoma	1.3
	Pericarditis traumatic	1.2
	Endocarditis	0.8
	Pneumonia-chronic	1.1
76 - 90	CSPD	1.4
	Endocarditis	2.2
	Pneumonia-chronic	2.9
	Pericarditis traumatic	2.2
	Abscessation	1.9
	Mucosal disease	0.8
91 - 95	Abscessation	3.1
	Endocarditis	2.3
	Mucosal disease	1.2
	Posterior vena caval thrombus	5.3
96 - 98	Endocarditis	8.0
	Posterior vena caval thrombus	9.2
	Pyelonephritis	9.6
99 - max.	CSPD	6.6
	Endocarditis	12.1

*Chronic suppurative pulmonary disease

Table IV-1 Biochemical Factor calculated for the most common diagnoses within each irregular percentile band for total protein, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Johne's disease	12.4
2 - 5	Johne's disease	6.9
	Abscessation	2.8
	CSPD*	1.2
	Endocarditis	2.1
	Mucosal disease	1.1
6 - 10	Johne's disease	3.0
	Endocarditis	2.6
	CSPD	1.0
11 - 25	Endocarditis	3.2
	CSPD	1.6
	Johne's disease	1.5
	Pericarditis traumatic	2.1
	Ostertagiasis	4.5
	Posterior vena caval thrombus	3.1
26 - 50	CSPD	1.3
	Mucosal disease	1.2
	Pericarditis traumatic	2.0
	Abscessation	1.6
	Johne's disease	1.1
51 - 75	CSPD	0.9
	Mucosal disease	0.9
	Congenital cardiac defect	1.8
	Abscessation	1.2
	Lymphosarcoma	0.8
	Osteomyelitis	2.7
	Pneumonia-chronic	1.1
76 - 90	Lymphosarcoma	2.6
	Mucosal disease	1.1
	CSPD	0.8
	Congenital cardiac defect	1.2
	Cerebellar hypoplasia	3.4
	Pneumonia	1.7
91 - 95	Mucosal disease	2.9
	Arthritis	3.3
	Enteritis	11.6
	Lymphosarcoma	2.1
	Spastic paresis	9.6
96 - 98	Mucosal disease	1.4
	Lymphosarcoma	1.9
99 - max.	Mucosal disease	5.1

*Chronic suppurative pulmonary disease

Table IV-2 Biochemical Factor calculated for the most common diagnoses within each irregular percentile band for albumin, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Bladder-rupture	45.4
	Lymphosarcoma	3.2
	Omphalophlebitis	45.4
	Reticulitis	45.4
2 - 5	Lymphosarcoma	4.3
	Congenital cardiac defect	2.5
	Johne's disease	1.7
	Pneumonia	4.6
6 - 10	Congenital cardiac defect	4.0
	Mucosal disease	1.2
	Malignant catarrhal fever	7.4
	Johne's disease	1.0
11 - 25	Mucosal disease	1.6
	Johne's disease	1.8
	CSPD*	0.8
26 - 50	Mucosal disease	1.4
	Johne's disease	1.8
	Congenital cardiac defect	1.4
	CSPD	0.6
	Lymphosarcoma	1.0
51 - 75	CSPD	1.2
	Mucosal disease	0.8
	Pericarditis traumatic	2.1
	Endocarditis	0.9
	Lymphosarcoma	1.0
76 - 90	CSPD	2.0
	Endocarditis	2.0
	Pericarditis traumatic	2.6
	Mucosal disease	0.8
	Pneumonia-chronic	2.1
91 - 95	CSPD	1.7
	Endocarditis	3.2
	Posterior vena caval thrombus	7.2
	Abscessation	3.3
	Pyelonephritis	6.0
96 - 98	Endocarditis	9.2
	Posterior vena caval thrombus	8.8
	Abscessation	2.4
	Actinobacillosis	13.4
	Arthritis	3.1
99 - max.	CSPD	26.5

*Chronic suppurative pulmonary disease

Table IV-3 Biochemical Factor calculated for the most common diagnoses within each irregular percentile band for globulin, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Mucosal disease	12.1
2 - 5	Mucosal disease	3.0
6 - 10	Mucosal disease	3.1
	Endocarditis	1.6
	Johne's disease	1.4
	Pericarditis traumatic	2.2
	CSPD*	0.6
	Ostertagiasis	3.4
11 - 25	Endocarditis	2.5
	Mucosal disease	1.3
	Pericarditis traumatic	2.8
	Abscessation	1.7
	CSPD	0.6
26 - 50	CSPD	1.1
	Lymphosarcoma	1.6
	Mucosal disease	0.7
	Abscessation	1.5
	Congenital cardiac defect	1.2
	Johne's disease	0.8
51 - 75	CSPD	1.5
	Endocarditis	1.1
	Johne's disease	1.0
	Lymphosarcoma	1.2
	Mucosal disease	0.6
76 - 90	CSPD	1.0
	Johne's disease	1.3
	Ulceration abomasal	3.6
	Congenital cardiac defect	1.3
	Lymphosarcoma	1.0
	Mucosal disease	0.5
	Pneumonia	2.4
91 - 95	Congenital cardiac defect	4.0
	CSPD	1.1
	Johne's disease	1.7
	Pneumonia-chronic	2.7
96 - 98	Abscessation	2.8
	Arthritis	3.6
	Mucosal disease	1.0
99 - max.	Bladder-rupture	51.2
	Ostertagiasis	11.3
	Pneumonia-chronic	5.0

*Chronic suppurative pulmonary disease

Table IV-4 Biochemical Factor calculated for the most common diagnoses within each irregular percentile band for potassium, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Mucosal disease	3.4
2 - 5	Mucosal disease	2.2
	Bladder-rupture	29.9
	Carcinoma	8.5
	Johne's disease	1.8
	Pericarditis traumatic	2.8
6 - 10	Mucosal disease	1.6
	Lymphosarcoma	2.4
	Pneumonia-chronic	3.3
11 - 25	Mucosal disease	2.2
	CSPD*	1.4
	Johne's disease	1.9
	Pericarditis traumatic	2.6
	Endocarditis	1.6
26 - 50	CSPD	1.5
	Endocarditis	1.3
	Lymphosarcoma	1.4
	Abscessation	1.5
	Mucosal disease	0.6
51 - 75	Mucosal disease	0.8
	Endocarditis	1.3
	Arthritis	2.1
	Abscessation	1.4
	CSPD	0.5
	Johne's disease	0.8
76 - 90	CSPD	1.0
	Johne's disease	1.6
	Mucosal disease	0.8
	Lymphosarcoma	1.3
	Ostertagiasis	2.9
91 - 95	Arthritis	2.1
	Cirrhosis	18.4
	CSPD	0.7
	Enteritis	7.3
96 - 98	Pneumonia	8.4
	CSPD	1.2
	Johne's disease	2.0
	Lymphosarcoma	2.3
	Mucosal disease	1.1
99 - max.	CSPD	9.1

*Chronic suppurative pulmonary disease

Table IV-5 Biochemical Factor calculated for the most common diagnoses within each irregular percentile band for chloride, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Arthritis	20.6
2 - 5	Mucosal disease	2.2
	Abscessation	4.1
	CSPD*	1.1
	Pericarditis traumatic	2.8
	Pyelonephritis	6.6
6 - 10	Endocarditis	3.0
	Johne's disease	2.5
	Mucosal disease	1.0
	Pneumonia-chronic	2.8
11 - 25	Mucosal disease	1.4
	Johne's disease	2.1
	Abscessation	2.2
	CSPD	0.8
26 - 50	Mucosal disease	1.2
	CSPD	1.0
	Lymphosarcoma	1.4
	Endocarditis	1.3
	Johne's disease	1.0
51 - 75	Mucosal disease	0.9
	CSPD	0.9
	Lymphosarcoma	1.2
	Posterior vena caval thrombus	2.3
	Endocarditis	0.9
	Johne's disease	0.8
	Pneumonia-chronic	1.2
76 - 90	CSPD	1.9
	Congenital cardiac defect	1.9
	Mucosal disease	0.7
	Cerebellar hypoplasia	4.4
	Pericarditis traumatic	1.2
	Pneumonia	2.2
	Pneumonia-chronic	1.3
91 - 95	CSPD	1.1
	Mucosal disease	1.0
	Neuropathy-peripheral	19.4
	Pneumonia	3.2
96 - 98	Congenital cardiac defect	2.4
	CSPD	0.9
	Ostertagiasis	5.6
99 - max.	Nephrosclerosis-juvenile	59.7

*Chronic suppurative pulmonary disease

Table IV-6 Biochemical Factor calculated for the most common diagnoses within each irregular percentile band for alkaline phosphatase, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Dentition poor	70.0
2 - 5	Johne's disease	6.2
	Mucosal disease	2.1
	CSPD*	1.1
	Endocarditis	1.9
	Lymphosarcoma	2.0
6 - 10	Johne's disease	3.9
	Mucosal disease	1.4
	CSPD	1.1
	Carcinoma	4.7
	Endocarditis	1.3
	Pericarditis traumatic	1.8
	Pneumonia-chronic	1.9
11 - 25	Johne's disease	2.5
	Endocarditis	2.4
	CSPD	0.9
	Mucosal disease	0.7
	Carcinoma	3.8
	Ostertagiasis	3.8
	Pericarditis traumatic	1.4
26 - 50	Mucosal disease	1.5
	Pericarditis traumatic	1.9
	Abscessation	1.7
	CSPD	0.7
	Lymphosarcoma	1.1
51 - 75	CSPD	1.5
	Lymphosarcoma	2.1
	Mucosal disease	0.8
	Abscessation	1.6
	Endocarditis	0.9
76 - 90	CSPD	1.0
	Congenital cardiac defect	2.2
	Mucosal disease	0.6
	Pneumonia-chronic	1.8
	Pneumonia	2.3
	Spastic paresis	4.7
91 - 95	CSPD	1.3
	Arthritis	3.1
	Fracture	6.2
96 - 98	Arthritis	3.5
	Mucosal disease	0.9
99 - max.	Congenital cardiac defect	18.0

*Chronic suppurative pulmonary disease

Table IV-7 Biochemical Factor calculated for the most common diagnoses within each irregular percentile band for calcium, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Dentition poor	57.5
	Mucosal disease	2.0
	Nephritis	57.5
	Pneumonia	10.3
	Posterior vena caval thrombus	9.4
	Pyelonephritis	12.6
2 - 5	CSPD*	2.8
	Pericarditis traumatic	3.7
	Carcinoma	8.5
	Endocarditis	1.7
	Posterior vena caval thrombus	4.2
6 - 10	Endocarditis	3.5
	CSPD	1.7
	Mucosal disease	1.5
	Abscessation	2.3
	Pericarditis traumatic	2.3
11 - 25	Mucosal disease	1.3
	CSPD	1.1
	Endocarditis	1.6
	Johne's disease	1.4
	Lymphosarcoma	1.4
	Posterior vena caval thrombus	3.3
26 - 50	CSPD	1.1
	Lymphosarcoma	1.6
	Mucosal disease	0.7
	Endocarditis	1.1
	Johne's disease	0.9
51 - 75	Johne's disease	1.8
	CSPD	0.9
	Mucosal disease	0.8
	Congenital cardiac defect	1.6
76 - 90	Mucosal disease	1.0
	CSPD	0.8
	Pericarditis traumatic	1.6
91 - 95	Lymphosarcoma	1.8
	Mucosal disease	0.9
	Spastic paresis	8.2
96 - 98	Mucosal disease	2.1
	Bladder-rupture	27.6
	Enteritis	11.0
99 - max.	Mucosal disease	4.0

*Chronic suppurative pulmonary disease

Table IV-8 Biochemical Factor calculated for the most common diagnoses within each irregular percentile band for magnesium, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Cirrhosis	57.0
	CSPD*	2.2
	Ostertagiasis	14.1
2 - 5	Abscessation	6.1
	Endocarditis	3.4
	Actinobacillosis	18.3
	Congenital cardiac defect	2.3
6 - 10	Mucosal disease	1.3
	Abscessation	2.6
	Cardiomyopathy	7.4
	Endocarditis	1.2
	Pneumonia-chronic	1.9
11 - 25	Endocarditis	2.2
	Pericarditis traumatic	2.1
	CSPD	0.7
	Mucosal disease	0.6
26 - 50	CSPD	1.2
	Mucosal disease	0.7
	Lymphosarcoma	1.3
	Pericarditis traumatic	1.7
	Johne's disease	0.9
51 - 75	CSPD	1.3
	Mucosal disease	1.0
	Johne's disease	1.1
	Pneumonia-chronic	1.6
	Arthritis	1.6
	Lymphosarcoma	0.8
76 - 90	CSPD	1.2
	Mucosal disease	0.9
	Johne's disease	1.2
	Lymphosarcoma	1.4
91 - 95	Mucosal disease	1.8
	Lymphosarcoma	3.0
	Congenital cardiac defect	2.9
	Bladder-rupture	19.5
	Hepatic abscessation	5.5
	Pyelonephritis	4.3
96 - 98	Mucosal disease	2.1
	Johne's disease	2.8
	Cardiomyopathy	11.4
	Peritonitis	7.1
99 - max.	Mucosal disease	9.2

*Chronic suppurative pulmonary disease

Table IV-9 Biochemical Factor calculated for the most common diagnoses within each irregular percentile band for phosphate, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Abscessation	5.5
	Bladder-rupture	56.3
	Mucosal disease	2.0
	Pneumonia	9.3
2 - 5	Mucosal disease	3.6
	Abscessation	5.1
	Congenital cardiac defect	2.5
	Tendons contracted	16.1
6 - 10	Congenital cardiac defect	3.5
	CSPD*	1.3
	Mucosal disease	1.2
	Endocarditis	1.7
	Osteomyelitis	7.2
11 - 25	Mucosal disease	1.2
	CSPD	0.8
	Abscessation	1.6
	Arthritis	2.0
	Pneumonia-chronic	1.6
26 - 50	CSPD	1.3
	Johne's disease	1.1
	Congenital cardiac defect	1.5
	Mucosal disease	0.5
	Arthritis	1.5
51 - 75	CSPD	1.2
	Mucosal disease	1.0
	Johne's disease	1.3
	Pericarditis traumatic	1.6
	Endocarditis	1.0
	Posterior vena caval thrombus	2.1
76 - 90	Lymphosarcoma	3.2
	Mucosal disease	1.2
	Endocarditis	2.3
	Johne's disease	1.3
	Pneumonia	2.9
91 - 95	Endocarditis	3.4
	Johne's disease	2.7
	CSPD	1.2
96 - 98	Lymphosarcoma	4.4
	CSPD	1.4
	Endocarditis	2.7
99 - max.	Pericarditis traumatic	12.5

*Chronic suppurative pulmonary disease

Table IV-10 Biochemical Factor calculated for the most common diagnoses within each irregular percentile band for aspartate amino-transferase, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 10	CSPD*	1.9
	Abscessation	1.8
	Congenital cardiac defect	1.5
	Johne's disease	1.2
	Mucosal disease	0.5
11 - 25	Mucosal disease	1.1
	CSPD	0.9
	Johne's disease	1.4
	Congenital cardiac defect	1.5
	Arthritis	1.9
	Pneumonia-chronic	1.5
26 - 50	Mucosal disease	1.3
	CSPD	1.4
	Pneumonia-chronic	3.1
	Endocarditis	1.4
	Abscessation	1.1
51 - 75	Mucosal disease	1.0
	Lymphosarcoma	1.5
	Johne's disease	1.1
	CSPD	0.6
	Congenital cardiac defect	1.1
	Endocarditis	0.9
76 - 90	Mucosal disease	1.5
	Lymphosarcoma	1.7
	CSPD	0.8
	Endocarditis	1.3
	Johne's disease	1.3
	Pericarditis traumatic	1.7
91 - 95	Endocarditis	3.9
	Pericarditis traumatic	3.9
	Mucosal disease	1.0
	Carcinoma	5.7
96 - 98	Pericarditis traumatic	8.0
	Endocarditis	3.3
	Lymphosarcoma	2.2
	Mucosal disease	1.0
99 - max.	Lymphosarcoma	8.1

*Chronic suppurative pulmonary disease

Table IV-11 Biochemical Factor calculated for the most common diagnoses within each irregular percentile band for bilirubin, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 1	Arthritis	5.0
	Dentition poor	40.6
	Dermatophytosis	40.6
	Spastic paresis	16.2
2 - 5	CSPD*	2.3
	Mucosal disease	2.0
	Pneumonia-chronic	6.5
	Abscessation	4.2
6 - 10	CSPD	3.1
	Endocarditis	2.2
	Abscessation	1.9
	Arthritis	2.3
	Congenital cardiac defect	1.8
	Johne's disease	1.2
	Pneumonia-chronic	2.1
11 - 25	CSPD	1.3
	Mucosal disease	1.0
	Pericarditis traumatic	1.6
	Endocarditis	1.0
	Pneumonia-chronic	1.5
26 - 50	CSPD	1.0
	Johne's disease	1.1
	Mucosal disease	0.6
	Arthritis	1.8
	Endocarditis	1.0
51 - 75	Mucosal disease	1.0
	Johne's disease	1.6
	CSPD	0.9
	Congenital cardiac defect	1.7
	Lymphosarcoma	1.0
76 - 90	Mucosal disease	1.1
	Lymphosarcoma	2.1
	CSPD	0.6
	Endocarditis	1.1
91 - 95	Endocarditis	3.6
	Enteritis	8.6
	Lymphosarcoma	1.7
	Mucosal disease	0.8
96 - 98	Mucosal disease	3.9
	Johne's disease	1.9
99 - max.	Bladder-rupture	162.3

*Chronic suppurative pulmonary disease

Table IV-12 Biochemical Factor calculated for the most common diagnoses within each irregular percentile band for creatinine, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 10	Johne's disease	3.8
	Congenital cardiac defect	1.9
	Lymphosarcoma	1.6
	Mucosal disease	0.8
	Ostertagiasis	3.8
11 - 20	Johne's disease	2.2
	Mucosal disease	1.3
	CSPD*	0.9
	Ostertagiasis	5.2
21 - 30	Johne's disease	2.3
	Mucosal disease	1.3
	CSPD	1.2
	Abscessation	1.4
	Congenital cardiac defect	1.4
31 - 40	Mucosal disease	1.0
	CSPD	0.8
	Spastic paresis	5.5
41 - 50	Mucosal disease	1.4
	Congenital cardiac defect	2.3
	CSPD	0.8
	Lymphosarcoma	1.5
	Pericarditis traumatic	1.9
51 - 60	Mucosal disease	0.8
	CSPD	0.6
	Lymphosarcoma	1.3
	Pericarditis traumatic	1.6
	Pneumonia-chronic	1.7
61 - 70	CSPD	1.3
	Mucosal disease	1.3
	Endocarditis	1.9
71 - 80	CSPD	2.4
	Lymphosarcoma	2.3
	Pneumonia-chronic	2.6
	Mucosal disease	0.7
81 - 90	CSPD	1.7
	Endocarditis	2.0
	Pericarditis traumatic	2.6
91 - max.	Endocarditis	5.2
	Posterior vena caval thrombus	6.3
	Mucosal disease	1.0
	Abscessation	2.0
	Pyelonephritis	5.0

*Chronic suppurative pulmonary disease

Table IV-13 Biochemical Factor calculated for the most common diagnoses within each regular percentile band for total protein, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 10	Johne's disease	5.3
	Endocarditis	2.0
	CSPD*	0.9
11 - 20	CSPD	2.0
	Endocarditis	3.7
	Ostertagiasis	6.2
	Posterior vena caval thrombus	4.3
	Johne's disease	1.1
21 - 30	Pericarditis traumatic	3.7
	CSPD	1.3
	Mucosal disease	1.3
	Johne's disease	1.8
31 - 40	CSPD	1.4
	Arthritis	3.2
	Endocarditis	1.5
	Mucosal disease	0.8
	Pericarditis traumatic	2.0
41 - 50	Mucosal disease	1.5
	CSPD	0.7
	Pneumonia-chronic	1.9
51 - 60	Mucosal disease	0.9
	Abscessation	1.8
	CSPD	0.8
	Pyelonephritis	3.4
61 - 70	Congenital cardiac defect	2.7
	CSPD	1.1
	Mucosal disease	0.9
	Lymphosarcoma	0.9
	Osteomyelitis	3.1
71 - 80	Lymphosarcoma	2.7
	Mucosal disease	1.0
81 - 90	Lymphosarcoma	2.2
	Mucosal disease	1.1
	CSPD	0.7
	Cerebellar hypoplasia	4.8
91 - max.	Mucosal disease	2.4
	Lymphosarcoma	1.7
	Enteritis	7.1
	Spastic paresis	5.9

*Chronic suppurative pulmonary disease

Table IV-14 Biochemical Factor calculated for the most common diagnoses within each regular percentile band for albumin, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 10	Congenital cardiac defect	3.0
	Lymphosarcoma	1.7
	Johne's disease	1.1
	Mucosal disease	0.7
	Malignant catarrhal fever	3.9
11 - 20	Mucosal disease	2.0
	Johne's disease	2.0
	CSPD*	0.9
	Lymphosarcoma	1.3
	Enteritis	5.5
21 - 30	Mucosal disease	1.2
	Johne's disease	1.5
	Arthritis	1.7
	CSPD	0.5
	Ostertagiasis	3.2
	Ulceration abomasal	2.8
31 - 40	Mucosal disease	1.3
	Johne's disease	1.4
41 - 50	Mucosal disease	1.6
	Johne's disease	2.3
	CSPD	1.0
	Pneumonia-chronic	2.1
	Congenital cardiac defect	1.4
51 - 60	CSPD	1.6
	Abscessation	1.6
	Pericarditis traumatic	1.6
61 - 70	Pericarditis traumatic	2.6
	Endocarditis	1.5
	Mucosal disease	0.8
71 - 80	CSPD	2.3
	Mucosal disease	1.5
	Lymphosarcoma	1.5
	Pneumonia-chronic	2.0
	Posterior vena caval thrombus	3.1
81 - 90	CSPD	1.6
	Endocarditis	2.9
	Pericarditis traumatic	3.9
91 - max.	Endocarditis	5.5
	Posterior vena caval thrombus	7.5
	CSPD	1.4
	Abscessation	2.8
	Pyelonephritis	4.5

*Chronic suppurative pulmonary disease

Table IV-15 Biochemical Factor calculated for the most common diagnoses within each regular percentile band for globulin, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 10	Mucosal disease	3.5
	Johne's disease	1.3
	Endocarditis	1.2
	Pericarditis traumatic	1.6
11 - 20	Endocarditis	3.3
	Mucosal disease	1.1
	Pericarditis traumatic	3.0
21 - 30	Johne's disease	1.8
	Mucosal disease	0.9
	Abscessation	1.8
	Pericarditis traumatic	1.8
31 - 40	CSPD*	1.5
	Mucosal disease	1.3
	Lymphosarcoma	1.9
	Abscessation	1.9
	Endocarditis	1.4
41 - 50	CSPD	1.1
	Abscessation	1.5
	Actinobacillosis	8.3
	Johne's disease	1.0
	Lymphosarcoma	1.2
	Mucosal disease	0.6
51 - 60	CSPD	1.3
	Lymphosarcoma	2.1
	Mucosal disease	0.8
	Johne's disease	1.1
	Pneumonia-chronic	1.8
61 - 70	CSPD	2.6
71 - 80	CSPD	0.7
	Johne's disease	1.1
	Endocarditis	0.9
	Ostertagiasis	3.1
	Posterior vena caval thrombus	2.3
	Pyelonephritis	3.1
81 - 90	CSPD	1.1
	Johne's disease	1.7
	Congenital cardiac defect	2.1
	Pneumonia	3.7
	Ulceration abomasal	4.5
91 - max.	Congenital cardiac defect	2.3

*Chronic suppurative pulmonary disease

Table IV-16 Biochemical Factor calculated for the most common diagnoses within each regular percentile band for potassium, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 10	Mucosal disease	2.2
	Lymphosarcoma	1.5
	Pneumonia-chronic	2.1
11 - 20	Mucosal disease	2.7
	CSPD*	1.5
	Johne's disease	2.3
	Pericarditis traumatic	2.5
	Endocarditis	1.4
21 - 30	CSPD	1.5
	Endocarditis	2.5
	Congenital cardiac defect	2.4
	Mucosal disease	0.9
31 - 40	Congenital cardiac defect	2.5
	CSPD	0.8
	Lymphosarcoma	1.5
41 - 50	CSPD	1.9
	Abscessation	1.9
	Mucosal disease	0.7
	Lymphosarcoma	1.2
51 - 60	Abscessation	2.6
	Endocarditis	1.6
	CSPD	0.7
	Congenital cardiac defect	1.3
	Fracture	4.0
61 - 70	Mucosal disease	1.0
	Arthritis	2.5
71 - 80	Arthritis	2.7
	Mucosal disease	0.8
	Endocarditis	1.2
	Johne's disease	1.1
	Posterior vena caval thrombus	3.1
81 - 90	CSPD	1.2
	Johne's disease	2.0
	Mucosal disease	1.1
	Lymphosarcoma	1.3
91 - max.	CSPD	1.3
	Pneumonia	3.6
	Arthritis	1.8
	Johne's disease	1.0
	Mucosal disease	0.5

*Chronic suppurative pulmonary disease

Table IV-17 Biochemical Factor calculated for the most common diagnoses within each regular percentile band for chloride, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 10	Mucosal disease	1.3
	Johne's disease	1.7
11 - 20	Mucosal disease	1.7
	Johne's disease	2.4
	CSPD*	0.8
	Ostertagiasis	4.7
	Pericarditis traumatic	2.0
	Ulceration abomasal	4.2
21 - 30	Abscessation	3.6
	Mucosal disease	1.2
	CSPD	1.0
	Lymphosarcoma	2.0
31 - 40	Mucosal disease	1.1
	Johne's disease	1.8
	Congenital cardiac defect	2.2
	CSPD	0.9
41 - 50	Mucosal disease	1.0
	CSPD	0.9
	Enteritis	7.1
	Pericarditis traumatic	1.7
	Reticulitis traumatic	5.1
51 - 60	Mucosal disease	1.1
	Johne's disease	1.6
	Lymphosarcoma	1.9
	CSPD	0.7
	Posterior vena caval thrombus	3.1
61 - 70	CSPD	1.2
	Mucosal disease	0.7
	Pneumonia-chronic	2.1
	Abscessation	1.4
	Pericarditis traumatic	1.4
71 - 80	CSPD	1.5
	Congenital cardiac defect	2.7
	Arthritis	1.9
	Endocarditis	1.2
81 - 90	CSPD	1.6
	Mucosal disease	1.1
	Cerebellar hypoplasia	6.8
	Pneumonia-chronic	2.0
91 - max.	CSPD	0.9
	Congenital cardiac defect	1.4
	Mucosal disease	0.5

*Chronic suppurative pulmonary disease

Table IV-18 Biochemical Factor calculated for the most common diagnoses within each regular percentile band for alkaline phosphatase, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 10	Johne's disease	4.3
	Mucosal disease	1.6
	CSPD*	0.9
	Endocarditis	1.3
11 - 20	Johne's disease	3.4
	Endocarditis	2.3
	CSPD	1.1
	Mucosal disease	1.0
21 - 30	Endocarditis	2.0
	Pericarditis traumatic	2.3
	Posterior vena caval thrombus	3.2
31 - 40	Mucosal disease	2.7
	Abscessation	2.5
	Johne's disease	1.0
	Lymphosarcoma	1.1
	Osteomyelitis	3.8
	Pericarditis traumatic	1.4
41 - 50	CSPD	1.1
	Mucosal disease	1.0
	Pericarditis traumatic	2.1
	Posterior vena caval thrombus	3.7
51 - 60	CSPD	1.3
	Abscessation	2.0
	Lymphosarcoma	1.5
61 - 70	CSPD	2.2
	Lymphosarcoma	2.4
	Mucosal disease	1.2
	Pneumonia-chronic	2.7
	Arthritis	2.7
71 - 80	Abscessation	2.1
	CSPD	0.9
	Lymphosarcoma	1.6
	Mucosal disease	0.8
81 - 90	CSPD	1.1
	Congenital cardiac defect	1.9
	Mucosal disease	0.6
	Spastic paresis	6.3
91 - max.	Arthritis	2.8
	Congenital cardiac defect	2.1
	CSPD	0.8
	Mucosal disease	0.5

*Chronic suppurative pulmonary disease

Table IV-19 Biochemical Factor calculated for the most common diagnoses within each regular percentile band for calcium, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 10	CSPD*	1.9
	Endocarditis	2.5
	Mucosal disease	1.1
	Pericarditis traumatic	2.6
11 - 20	Endocarditis	2.1
	CSPD	1.0
	Johne's disease	1.5
	Lymphosarcoma	1.8
	Mucosal disease	0.9
21 - 30	Mucosal disease	1.7
	Posterior vena caval thrombus	4.8
	Abscessation	2.1
	CSPD	0.9
	Johne's disease	1.4
31 - 40	CSPD	2.0
	Endocarditis	2.0
	Johne's disease	1.8
	Lymphosarcoma	2.1
41 - 50	Lymphosarcoma	1.9
	Osteomyelitis	5.3
51 - 60	Johne's disease	2.3
	CSPD	1.3
	Pneumonia-chronic	2.2
	Endocarditis	1.0
	Mucosal disease	0.5
61 - 70	Congenital cardiac defect	3.0
	Johne's disease	1.3
	Mucosal disease	0.7
71 - 80	CSPD	1.2
	Mucosal disease	0.8
	Congenital cardiac defect	2.0
	Johne's disease	1.1
81 - 90	Mucosal disease	1.5
	Pericarditis traumatic	1.6
	Ulceration abomasal	3.7
	CSPD	0.4
	Johne's disease	0.7
91 - max.	Mucosal disease	1.7
	Lymphosarcoma	1.2
	Pericarditis traumatic	1.5

*Chronic suppurative pulmonary disease

Table IV-20 Biochemical Factor calculated for the most common diagnoses within each regular percentile band for magnesium, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 10	Abscessation	3.7
	Endocarditis	1.9
	Mucosal disease	0.8
11 - 20	Endocarditis	2.6
	CSPD*	1.0
	Diffuse fibrosing alveolitis	8.4
21 - 30	Pericarditis traumatic	2.8
	Mucosal disease	0.8
	Pneumonia-chronic	2.3
31 - 40	CSPD	1.8
	Mucosal disease	1.0
	Pericarditis traumatic	2.4
	Pneumonia	3.0
	Pneumonia-chronic	1.8
41 - 50	Lymphosarcoma	1.8
	CSPD	0.8
	Johne's disease	1.3
	Ulceration abomasal	4.5
51 - 60	CSPD	1.7
	Mucosal disease	1.0
	Endocarditis	1.3
61 - 70	Mucosal disease	1.3
	Pneumonia-chronic	2.8
	Lymphosarcoma	1.5
	Cerebellar hypoplasia	5.2
	CSPD	0.6
71 - 80	CSPD	1.3
	Johne's disease	1.7
	Mucosal disease	0.9
	Abscessation	1.4
	Endocarditis	1.0
	Peritonitis	3.9
81 - 90	CSPD	1.7
	Lymphosarcoma	2.1
	Johne's disease	1.4
	Mucosal disease	0.8
91 - max.	Mucosal disease	2.5
	Johne's disease	1.2
	Lymphosarcoma	1.4
	Congenital cardiac defect	1.4
	Hepatic abscessation	4.2

*Chronic suppurative pulmonary disease

Table IV-21 Biochemical Factor calculated for the most common diagnoses within each regular percentile band for phosphate, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 10	Mucosal disease	2.2
	Abscessation	3.1
	Congenital cardiac defect	2.7
11 - 20	Mucosal disease	1.7
	Abscessation	2.4
	CSPD*	0.7
21 - 30	CSPD	1.2
	Arthritis	2.5
	Pneumonia-chronic	2.0
31 - 40	CSPD	2.5
	Arthritis	1.9
	Congenital cardiac defect	1.6
	Pneumonia	2.6
	Ulceration abomasal	3.5
41 - 50	Johne's disease	2.0
	Mucosal disease	0.7
51 - 60	Mucosal disease	1.2
	CSPD	1.1
	Johne's disease	1.3
	Pericarditis traumatic	2.0
61 - 70	CSPD	1.4
	Mucosal disease	1.1
	Johne's disease	1.2
	Ostertagiasis	5.0
71 - 80	Mucosal disease	1.3
	Endocarditis	2.4
	Johne's disease	1.9
	CSPD	0.9
81 - 90	Lymphosarcoma	3.9
	Endocarditis	2.0
	Mucosal disease	0.7
	Johne's disease	0.9
	Malignant catarrhal fever	4.4
	Ostertagiasis	3.8
91 - max.	Endocarditis	2.7
	CSPD	1.1
	Lymphosarcoma	2.3
	Pericarditis traumatic	2.7
	Johne's disease	1.4

*Chronic suppurative pulmonary disease

Table IV-22 Biochemical Factor calculated for the most common diagnoses within each regular percentile band for aspartate amino-transferase, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 20	CSPD*	1.6
	Abscessation	1.6
	Congenital cardiac defect	1.6
	Johne's disease	1.2
	Mucosal disease	0.5
21 - 30	Mucosal disease	2.7
	Johne's disease	2.1
	Fracture	7.7
	Peritonitis	4.8
	Pneumonia-chronic	2.0
31 - 50	Mucosal disease	1.3
	CSPD	1.4
	Pneumonia-chronic	3.1
	Endocarditis	1.4
	Abscessation	1.1
51 - 60	Johne's disease	2.5
	Mucosal disease	0.9
	Abscessation	1.1
	CSPD	0.6
	Lymphosarcoma	0.9
	Pyelonephritis	2.8
61 - 70	Mucosal disease	1.2
	CSPD	1.1
	Lymphosarcoma	1.8
	Congenital cardiac defect	1.6
	Malignant catarrhal fever	5.0
	Pericarditis traumatic	1.6
	Posterior vena caval thrombus	2.9
71 - 80	Mucosal disease	0.9
	Congenital cardiac defect	1.8
	Lymphosarcoma	1.5
	Pericarditis traumatic	1.9
81 - 90	Mucosal disease	1.7
	Lymphosarcoma	2.5
	Endocarditis	1.9
	CSPD	0.9
	Johne's disease	1.4
91 - max.	Pericarditis traumatic	4.7
	Endocarditis	3.2
	Mucosal disease	0.9
	Lymphosarcoma	1.5
	Carcinoma	4.4

*Chronic suppurative pulmonary disease

Table IV-23 Biochemical Factor calculated for the most common diagnoses within each regular percentile band for bilirubin, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent diagnoses	Biochemical Factor
Min. - 10	CSPD*	2.3
	Pneumonia-chronic	3.3
	Abscessation	2.4
	Mucosal disease	0.9
11 - 20	CSPD	1.7
	Mucosal disease	0.9
	Abscessation	1.5
	Pericarditis traumatic	1.4
	Pneumonia	2.9
	Pneumonia-chronic	1.7
21 - 30	Mucosal disease	0.8
	Pericarditis traumatic	2.1
	Endocarditis	1.3
31 - 40	CSPD	1.3
	Johne's disease	1.6
	Mucosal disease	0.9
	Posterior vena caval thrombus	4.0
41 - 50	CSPD	1.0
	Arthritis	2.4
	Johne's disease	1.3
	Lymphosarcoma	1.6
	Ostertagiasis	4.8
51 - 60	Congenital cardiac defect	3.0
	Johne's disease	1.6
	Mucosal disease	0.9
61 - 70	Mucosal disease	1.1
	Johne's disease	1.6
	CSPD	0.8
71 - 80	CSPD	1.2
	Mucosal disease	1.1
	Abscessation	2.0
	Endocarditis	1.5
81 - 90	Lymphosarcoma	3.1
	Mucosal disease	1.2
	Enteropathy-chronic lymphocytic	9.2
91 - max.	Mucosal disease	2.0
	Endocarditis	1.7
	Johne's disease	1.1
	Lymphosarcoma	1.3
	Bladder-rupture	10.8

*Chronic suppurative pulmonary disease

Table IV-24 Biochemical Factor calculated for the most common diagnoses within each regular percentile band for creatinine, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 1	Mouth	4.8
	Small intestine	2.9
2 - 5	Small intestine	7.0
	Multi-system	2.5
6 - 10	Small intestine	1.9
	Mouth	2.0
	Cardiovascular	0.5
	Lower respiratory	0.4
11 - 25	Small intestine	2.3
	Lower respiratory	0.7
	Mouth	1.5
	Cardiovascular	0.4
26 - 50	Lower respiratory	1.0
	Cardiovascular	0.9
	Multi-system	1.3
	Bones	1.3
51 - 75	Lower respiratory	1.4
	Cardiovascular	0.9
	Liver	2.4
	Bones	1.2
	Joints	1.5
76 - 90	Lower respiratory	1.8
	Cardiovascular	1.7
	Multi-system	0.8
	Bones	1.1
	Connective tissues	5.0
91 - 95	Cardiovascular	1.5
	Serosae	4.3
96 - 99	Cardiovascular	5.1
	Kidney	5.3
99 - max.	Lower respiratory	3.0
	Cardiovascular	2.9

Table IV-25 Biochemical Factor calculated for the most common pathological sites within each irregular percentile band for total protein, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 1	Small intestine	11.1
2 - 5	Small intestine	4.2
	Lower respiratory	1.1
	Cardiovascular	1.1
6 - 10	Cardiovascular	1.9
	Small intestine	1.8
	Lower respiratory	0.6
	Serosae	3.5
11 - 25	Cardiovascular	2.2
	Lower respiratory	1.5
	Small intestine	1.2
	Stomach	2.7
	Forestomachs	2.0
26 - 50	Lower respiratory	1.1
	Cardiovascular	1.1
	Multi-system	1.3
	Mouth	1.6
	Small intestine	0.9
51 - 75	Lower respiratory	1.0
	Cardiovascular	0.7
	Bones	1.6
	Mouth	1.2
76 - 90	Lower respiratory	0.9
	Multi-system	1.2
	Thymus	3.3
	Cardiovascular	0.5
	Brain	2.4
	Bones	1.6
91 - 95	Multi-system	3.5
	Lower respiratory	0.8
	Bones	2.9
96 - 99	Small intestine	1.5
	Bones	2.6
99 - max.	Multi-system	6.2

Table IV-26 Biochemical Factor calculated for the most common pathological sites within each irregular percentile band for albumin, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 1	Cardiovascular	1.7
2 - 5	Small intestine	2.2
	Lower respiratory	1.0
	Lymphatic	12.0
	Bones	1.8
	Cardiovascular	0.5
6 - 10	Mouth	4.0
	Cardiovascular	0.7
	Multi-system	1.1
	Small intestine	0.9
	Brain	2.5
11 - 25	Small intestine	2.1
	Lower respiratory	0.8
	Multi-system	1.3
	Brain	2.0
	Joints	1.6
26 - 50	Multi-system	1.8
	Small intestine	1.4
	Cardiovascular	0.6
	Lower respiratory	0.6
	Mouth	1.4
51 - 75	Lower respiratory	1.6
	Cardiovascular	1.0
	Multi-system	0.8
	Bones	1.2
	Small intestine	0.6
	Liver	2.1
	Joints	1.3
76 - 90	Lower respiratory	1.8
	Cardiovascular	1.6
	Bones	1.2
	Forestomachs	1.7
	Serosae	1.8
91 - 95	Cardiovascular	2.8
	Lower respiratory	1.2
	Kidney	3.3
	Serosae	3.3
	Larynx	7.1
96 - 99	Cardiovascular	5.5
	Forestomachs	3.1
	Lower respiratory	0.4
	Joints	2.2
99 - max.	Lower respiratory	12.0

Table IV-27 Biochemical Factor calculated for the most common pathological sites within each irregular percentile band for globulin, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 1	Multi-system	7.7
	Forestomachs	8.3
	Small intestine	2.6
	Other	14.2
2 - 5	Multi-system	2.4
	Small intestine	1.4
	Lower respiratory	0.7
6 - 10	Multi-system	3.0
	Cardiovascular	1.2
	Small intestine	1.5
	Lower respiratory	0.4
11 - 25	Cardiovascular	1.8
	Lower respiratory	1.0
	Multi-system	1.1
	Small intestine	0.8
26 - 50	Lower respiratory	1.0
	Cardiovascular	0.8
	Small intestine	1.0
	Multi-system	0.8
	Bones	1.3
51 - 75	Lower respiratory	1.4
	Cardiovascular	1.0
	Bones	1.4
	Mouth	1.1
	Small intestine	0.7
76 - 90	Lower respiratory	1.0
	Cardiovascular	0.6
	Small intestine	1.1
	Multi-system	0.8
	Stomach	2.4
91 - 95	Cardiovascular	2.0
	Lower respiratory	1.6
	Small intestine	1.5
96 - 99	Small intestine	2.4
	Mouth	2.9
	Joints	3.9
	Cardiovascular	0.8
99 - max.	Multi-system	2.2
	Stomach	6.7
	Lower respiratory	0.9
	Brain	5.0
	Reproductive, Female	20.4
	Lower urinary	14.5

Table IV-28 Biochemical Factor calculated for the most common pathological sites within each irregular percentile band for potassium, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 1	Multi-system	4.3
2 - 5	Small intestine	3.8
6 - 10	Lower respiratory	1.3
	Multi-system	1.4
	Thymus	3.9
11 - 25	Cardiovascular	1.6
	Lower respiratory	1.2
	Small intestine	1.4
	Multi-system	1.5
	Mouth	1.5
26 - 50	Cardiovascular	1.3
	Lower respiratory	1.3
	Multi-system	1.1
	Small intestine	0.5
	Bones	1.0
51 - 75	Cardiovascular	1.0
	Lower respiratory	0.8
	Bones	1.8
	Mouth	1.3
76 - 90	Lower respiratory	0.8
	Small intestine	1.5
	Cardiovascular	0.4
91 - 95	Cardiovascular	0.8
	Small intestine	1.4
	Lower respiratory	0.7
	Joints	3.1
	Mouth	1.7
96 - 99	Lower respiratory	1.6
	Small intestine	1.8
	Cardiovascular	0.9
	Multi-system	1.4
	Kidney	4.0
99 - max.	Lower respiratory	4.0

Table IV-29 Biochemical Factor calculated for the most common pathological sites within each irregular percentile band for chloride, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 1	Joints	15.1
2 - 5	Cardiovascular	1.1
	Multi-system	2.0
	Lower respiratory	0.8
6 - 10	Small intestine	1.9
	Lower respiratory	0.8
	Cardiovascular	0.9
	Mouth	2.4
11 - 25	Cardiovascular	1.2
	Small intestine	1.7
	Lower respiratory	0.8
	Multi-system	1.2
26 - 50	Lower respiratory	0.9
	Cardiovascular	0.9
	Small intestine	1.3
	Multi-system	1.3
51 - 75	Cardiovascular	1.2
	Lower respiratory	1.0
	Mouth	1.6
	Small intestine	0.8
	Multi-system	0.8
76 - 90	Lower respiratory	1.7
	Cardiovascular	1.0
	Small intestine	0.6
	Brain	1.6
	Joints	1.4
91 - 95	Lower respiratory	1.1
	Cardiovascular	0.5
96 - 99	Cardiovascular	0.9
	Stomach	5.2
	Liver	5.6
	Lower respiratory	0.7
99 - max.	Small intestine	2.2
	Bones	3.8
	Kidney	7.3
	Lower urinary	19.8

Table IV-30 Biochemical Factor calculated for the most common pathological sites within each irregular percentile band for alkaline phosphatase, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 1	Multi-system	3.1
	Mouth	4.3
	Kidney	8.6
	Lower urinary	17.4
2 - 5	Small intestine	5.5
	Lower respiratory	0.8
	Multi-system	1.2
	Lymphatic	5.5
	Cardiovascular	0.5
6 - 10	Small intestine	2.4
	Lower respiratory	1.1
	Cardiovascular	0.9
	Multi-system	1.3
11 - 25	Cardiovascular	1.7
	Small intestine	2.0
	Lower respiratory	0.8
26 - 50	Cardiovascular	1.6
	Lower respiratory	0.7
	Multi-system	1.6
	Small intestine	0.9
	Mouth	1.1
51 - 75	Lower respiratory	1.4
	Cardiovascular	0.6
	Bones	1.4
	Thymus	2.3
76 - 90	Lower respiratory	1.5
	Cardiovascular	0.7
	Bones	1.9
	Mouth	1.1
	Brain	1.7
	Muscle	2.9
91 - 95	Lower respiratory	1.3
	Bones	2.2
	Forestomachs	2.5
	Joints	2.1
96 - 99	Lower respiratory	0.7
	Brain	3.8
	Cardiovascular	0.7
99 - max.	Cardiovascular	3.1

Table IV-31 Biochemical Factor calculated for the most common pathological sites within each irregular percentile band for calcium, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 1	Mouth	8.5
	Kidney	16.9
2 - 5	Cardiovascular	3.2
	Lower respiratory	1.6
	Mouth	1.6
6 - 10	Cardiovascular	2.0
	Lower respiratory	1.3
11 - 25	Cardiovascular	1.3
	Lower respiratory	1.2
	Multi-system	1.4
	Small intestine	1.0
	Mouth	1.2
26 - 50	Lower respiratory	1.4
	Cardiovascular	0.9
	Bones	1.5
	Multi-system	0.9
51 - 75	Lower respiratory	0.8
	Cardiovascular	0.8
	Small intestine	1.6
	Brain	1.9
	Bones	1.1
76 - 90	Cardiovascular	0.7
	Multi-system	1.6
	Small intestine	1.2
	Lower respiratory	0.6
	Stomach	2.1
	Bones	0.9
91 - 95	Mouth	2.4
	Lower respiratory	0.7
	Cardiovascular	0.7
	Muscle	4.0
	Bones	1.6
96 - 99	Small intestine	2.2
	Multi-system	1.9
	Lower urinary	14.3
	Kidney	3.4
	Cardiovascular	0.5
99 - max.	Multi-system	2.2
	Forestomachs	6.9
	Small intestine	1.8
	Liver	6.4
	Cardiovascular	0.9
	Serosae	6.0

Table IV-32 Biochemical Factor calculated for the most common pathological sites within each irregular percentile band for magnesium, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 1	Stomach	8.6
	Liver	7.5
	Muscle	9.4
2 - 5	Cardiovascular	2.5
	Mouth	2.3
	Bones	2.5
	Lower respiratory	0.4
	Serosae	2.9
6 - 10	Cardiovascular	1.5
	Multi-system	2.1
	Lower respiratory	0.5
11 - 25	Cardiovascular	1.6
	Lower respiratory	1.3
	Small intestine	0.9
	Stomach	2.7
26 - 50	Cardiovascular	1.4
	Lower respiratory	1.0
	Small intestine	1.1
	Mouth	1.2
	Bones	1.2
51 - 75	Lower respiratory	1.3
	Cardiovascular	0.5
	Brain	2.7
	Multi-system	1.0
	Small intestine	0.9
76 - 90	Lower respiratory	1.0
	Cardiovascular	0.6
	Multi-system	1.2
	Mouth	1.7
	Small intestine	1.0
91 - 95	Cardiovascular	0.7
	Multi-system	1.3
	Small intestine	1.1
	Lower respiratory	0.5
	Lower urinary	10.0
96 - 99	Small intestine	2.3
	Lower respiratory	0.8
	Cardiovascular	0.8
99 - max.	Multi-system	7.3
	Small intestine	1.6
	Bones	2.9
	Kidney	5.2

Table IV-33 Biochemical Factor calculated for the most common pathological sites within each irregular percentile band for phosphate, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 1	Multi-system	2.5
	Lower respiratory	1.0
2 - 5	Small intestine	1.9
	Cardiovascular	0.9
	Multi-system	1.6
	Mouth	2.4
6 - 10	Cardiovascular	1.9
	Lower respiratory	0.8
	Bones	2.4
11 - 25	Lower respiratory	0.9
	Cardiovascular	0.7
	Multi-system	1.5
	Mouth	1.5
	Joints	1.8
26 - 50	Lower respiratory	1.2
	Cardiovascular	0.7
	Small intestine	0.9
51 - 75	Cardiovascular	1.1
	Lower respiratory	1.0
	Small intestine	1.3
	Bones	1.4
76 - 90	Lower respiratory	1.0
	Cardiovascular	1.0
	Small intestine	1.2
	Multi-system	1.3
	Thymus	2.6
91 - 95	Cardiovascular	2.4
	Lower respiratory	1.0
	Multi-system	1.9
	Small intestine	1.6
96 - 99	Lower respiratory	1.8
	Thymus	6.9
	Cardiovascular	1.0
	Muscle	6.4
99 - max.	Cardiovascular	4.5

Table IV-34 Biochemical Factor calculated for the most common pathological sites within each irregular percentile band for aspartate amino-transferase, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 10	Lower respiratory	1.4
	Cardiovascular	0.7
	Small intestine	1.0
	Multi-system	0.7
	Kidney	1.9
11 - 25	Lower respiratory	1.0
	Small intestine	1.3
	Bones	2.7
	Cardiovascular	0.6
	Multi-system	0.8
	Joints	2.0
26 - 50	Lower respiratory	1.4
	Cardiovascular	0.8
	Multi-system	1.1
	Mouth	1.2
	Small intestine	0.6
51 - 75	Cardiovascular	1.0
	Lower respiratory	0.8
	Mouth	1.8
	Small intestine	1.0
	Multi-system	0.9
76 - 90	Cardiovascular	1.4
	Multi-system	2.1
	Lower respiratory	0.7
	Small intestine	1.1
	Mouth	0.8
	Thymus	1.6
91 - 95	Cardiovascular	2.9
	Small intestine	1.2
	Multi-system	0.8
	Mouth	1.2
	Stomach	3.6
96 - 99	Cardiovascular	4.0
	Lower respiratory	0.6
	Thymus	3.4
99 - max.	Liver	18.0
	Thymus	12.6

Table IV-35 Biochemical Factor calculated for the most common pathological sites within each irregular percentile band for bilirubin, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 1	Joints	14.3
2 - 5	Lower respiratory	2.5
	Cardiovascular	1.1
	Multi-system	1.8
	Mouth	1.9
	Larynx	10.3
6 - 10	Lower respiratory	2.5
	Cardiovascular	1.4
	Serosae	3.7
	Small intestine	0.7
	Joints	1.6
11 - 25	Lower respiratory	1.3
	Cardiovascular	0.9
	Multi-system	1.6
	Other	3.3
	Mouth	1.0
26 - 50	Lower respiratory	1.1
	Cardiovascular	1.1
	Small intestine	1.0
	Joints	1.5
	Serosae	2.0
51 - 75	Cardiovascular	1.0
	Lower respiratory	0.8
	Small intestine	1.1
	Multi-system	1.1
	Bones	1.6
76 - 90	Cardiovascular	0.8
	Small intestine	1.4
	Lower respiratory	0.6
	Multi-system	1.1
91 - 95	Cardiovascular	1.7
	Multi-system	1.5
	Small intestine	1.3
	Bones	1.6
	Kidney	4.8
	Thymus	2.6
96 - 99	Small intestine	3.2
	Lower respiratory	0.9
	Cardiovascular	0.6
99 - max.	Lower urinary	92.0

Table IV-36 Biochemical Factor calculated for the most common pathological sites within each irregular percentile band for creatinine, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 10	Small intestine	3.4
	Mouth	2.2
	Multi-system	1.3
11 - 20	Small intestine	1.8
	Lower respiratory	0.7
	Stomach	3.9
	Mouth	1.4
21 - 30	Small intestine	2.1
	Lower respiratory	0.7
	Cardiovascular	0.7
	Multi-system	1.4
31 - 40	Lower respiratory	0.8
	Cardiovascular	0.8
	Brain	3.4
	Multi-system	1.0
	Small intestine	0.8
41 - 50	Lower respiratory	1.2
	Cardiovascular	1.1
	Multi-system	1.7
	Thymus	2.4
51 - 60	Lower respiratory	1.1
	Cardiovascular	0.7
	Multi-system	1.3
	Bones	1.9
61 - 70	Cardiovascular	1.1
	Lower respiratory	1.0
	Muscle	4.7
	Oesophagus	4.6
	Other	4.1
71 - 80	Lower respiratory	2.0
	Cardiovascular	1.0
	Thymus	3.1
81 - 90	Lower respiratory	2.0
	Cardiovascular	1.7
91 - max.	Cardiovascular	2.8
	Lower respiratory	0.5
	Multi-system	1.0
	Kidney	2.8

Table IV-37 Biochemical Factor calculated for the most common pathological sites within each regular percentile band for total protein, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 10	Small intestine	3.5
	Cardiovascular	1.3
	Lower respiratory	0.7
11 - 20	Cardiovascular	2.2
	Lower respiratory	1.7
	Stomach	3.7
	Small intestine	1.0
21 - 30	Cardiovascular	1.5
	Lower respiratory	1.2
	Multi-system	1.3
	Small intestine	1.1
31 - 40	Cardiovascular	1.1
	Lower respiratory	1.0
	Joints	2.6
	Multi-system	1.2
	Small intestine	1.0
41 - 50	Lower respiratory	1.1
	Cardiovascular	1.1
	Mouth	3.5
	Multi-system	1.2
51 - 60	Lower respiratory	0.9
	Bones	2.1
	Cardiovascular	0.5
	Small intestine	0.8
61 - 70	Cardiovascular	1.0
	Lower respiratory	0.9
	Mouth	1.9
71 - 80	Lower respiratory	0.8
	Multi-system	1.6
	Bones	2.4
81 - 90	Lower respiratory	1.1
	Brain	3.5
	Multi-system	1.1
	Thymus	2.9
	Cardiovascular	0.4
91 - max.	Multi-system	2.2
	Bones	2.9
	Small intestine	1.1
	Lower respiratory	0.5

Table IV-38 Biochemical Factor calculated for the most common pathological sites within each regular percentile band for albumin, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 10	Cardiovascular	0.7
	Mouth	2.4
	Small intestine	1.2
11 - 20	Small intestine	2.5
	Multi-system	1.5
	Lower respiratory	0.6
	Mouth	1.4
21 - 30	Small intestine	1.5
	Lower respiratory	0.7
	Brain	2.9
	Joints	2.4
	Multi-system	1.1
31 - 40	Multi-system	1.8
	Cardiovascular	0.7
	Mouth	2.1
	Small intestine	1.1
41 - 50	Lower respiratory	1.1
	Multi-system	1.9
	Small intestine	1.6
	Cardiovascular	0.6
51 - 60	Lower respiratory	1.5
	Cardiovascular	0.8
	Liver	2.3
	Bones	1.1
61 - 70	Lower respiratory	1.4
	Cardiovascular	1.3
	Multi-system	1.3
	Joints	2.4
71 - 80	Lower respiratory	2.4
	Cardiovascular	0.9
	Multi-system	0.9
	Small intestine	0.8
81 - 90	Cardiovascular	2.2
	Lower respiratory	1.2
	Forestomachs	2.7
	Serosae	2.9
91 - max.	Cardiovascular	3.7
	Lower respiratory	1.0
	Kidney	2.5

Table IV-39 Biochemical Factor calculated for the most common pathological sites within each regular percentile band for globulin, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 10	Multi-system	3.0
	Cardiovascular	0.8
	Small intestine	1.5
	Lower respiratory	0.5
11 - 20	Cardiovascular	2.1
	Lower respiratory	0.9
	Multi-system	1.4
	Mouth	1.2
	Liver	2.7
21 - 30	Cardiovascular	0.9
	Small intestine	1.5
	Lower respiratory	0.7
	Mouth	1.2
31 - 40	Lower respiratory	1.3
	Cardiovascular	1.2
	Multi-system	1.7
	Bones	1.7
41 - 50	Lower respiratory	1.0
	Small intestine	1.2
	Cardiovascular	0.6
	Mouth	1.3
	Skin	3.4
51 - 60	Lower respiratory	1.4
	Cardiovascular	0.7
	Bones	1.9
61 - 70	Lower respiratory	1.6
	Cardiovascular	0.7
	Joints	2.2
	Mouth	1.2
	Serosae	2.4
71 - 80	Cardiovascular	1.2
	Lower respiratory	0.8
	Stomach	2.5
	Small intestine	0.7
	Kidney	2.3
81 - 90	Lower respiratory	1.3
	Cardiovascular	0.8
	Small intestine	1.5
	Brain	2.2
91 - max.	Cardiovascular	1.2
	Lower respiratory	0.9
	Small intestine	1.7
	Joints	2.0

Table IV-40 Biochemical Factor calculated for the most common pathological sites within each regular percentile band for potassium, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 10	Lower respiratory	0.8
	Small intestine	1.4
	Multi-system	1.4
11 - 20	Cardiovascular	1.5
	Lower respiratory	1.4
	Multi-system	2.2
	Small intestine	1.6
21 - 30	Cardiovascular	2.0
	Lower respiratory	1.2
	Mouth	1.6
	Small intestine	0.9
31 - 40	Cardiovascular	1.3
	Lower respiratory	1.0
	Multi-system	1.4
	Brain	2.1
	Bones	1.4
41 - 50	Lower respiratory	1.4
	Cardiovascular	1.0
	Multi-system	0.9
51 - 60	Lower respiratory	0.9
	Cardiovascular	0.9
	Bones	2.9
	Mouth	1.4
61 - 70	Lower respiratory	0.8
	Cardiovascular	0.8
	Mouth	2.3
	Multi-system	0.9
	Joints	1.8
71 - 80	Cardiovascular	1.2
	Lower respiratory	0.7
	Small intestine	1.2
	Joints	1.9
	Bones	1.2
81 - 90	Lower respiratory	0.8
	Small intestine	1.4
	Multi-system	1.1
	Bones	1.6
91 - max.	Lower respiratory	1.1
	Cardiovascular	0.8
	Small intestine	1.4
	Joints	2.2

Table IV-41 Biochemical Factor calculated for the most common pathological sites within each regular percentile band for chloride, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 10	Cardiovascular	1.0
	Lower respiratory	0.8
	Small intestine	1.4
	Multi-system	1.4
11 - 20	Cardiovascular	1.4
	Small intestine	1.7
	Multi-system	1.6
	Lower respiratory	0.5
21 - 30	Lower respiratory	1.3
	Cardiovascular	0.8
	Small intestine	1.3
	Mouth	1.7
31 - 40	Cardiovascular	0.9
	Small intestine	1.6
	Lower respiratory	0.6
	Multi-system	1.4
41 - 50	Lower respiratory	1.0
	Cardiovascular	1.0
	Multi-system	1.6
	Small intestine	1.1
51 - 60	Cardiovascular	1.2
	Lower respiratory	0.9
	Small intestine	1.4
	Mouth	1.9
61 - 70	Lower respiratory	1.6
	Cardiovascular	0.9
	Bones	2.1
	Mouth	1.6
71 - 80	Cardiovascular	1.5
	Lower respiratory	1.0
	Joints	1.9
	Multi-system	0.7
	Bones	1.1
81 - 90	Lower respiratory	1.6
	Cardiovascular	1.0
	Brain	2.5
	Multi-system	0.9
91 - max.	Lower respiratory	0.8
	Cardiovascular	0.6
	Multi-system	0.8
	Liver	2.8
	Bones	1.3

Table IV-42 Biochemical Factor calculated for the most common pathological sites within each regular percentile band for alkaline phosphatase, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 10	Small intestine	3.1
	Lower respiratory	0.8
	Multi-system	1.5
	Cardiovascular	0.6
11 - 20	Cardiovascular	1.5
	Small intestine	2.8
	Lower respiratory	0.8
	Multi-system	1.0
	Stomach	3.4
21 - 30	Cardiovascular	2.5
	Lower respiratory	0.9
	Mouth	1.5
	Small intestine	0.7
	Serosae	2.4
31 - 40	Multi-system	2.8
	Cardiovascular	0.9
	Mouth	1.6
	Small intestine	1.0
41 - 50	Cardiovascular	1.8
	Lower respiratory	0.8
	Multi-system	1.2
	Small intestine	0.8
	Brain	2.2
51 - 60	Lower respiratory	1.3
	Cardiovascular	0.6
	Bones	1.4
	Kidney	2.6
61 - 70	Lower respiratory	1.8
	Cardiovascular	0.7
	Mouth	1.6
	Joints	2.6
	Thymus	3.0
71 - 80	Lower respiratory	1.4
	Bones	2.3
	Cardiovascular	0.6
	Thymus	2.6
81 - 90	Lower respiratory	1.3
	Cardiovascular	0.6
	Bones	1.9
91 - max.	Lower respiratory	0.9
	Cardiovascular	0.7

Table IV-43 Biochemical Factor calculated for the most common pathological sites within each regular percentile band for calcium, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 10	Cardiovascular	2.3
	Lower respiratory	1.4
	Mouth	1.4
11 - 20	Lower respiratory	1.4
	Cardiovascular	1.2
	Small intestine	1.1
21 - 30	Cardiovascular	1.3
	Multi-system	2.5
	Mouth	2.6
	Lower respiratory	0.7
31 - 40	Lower respiratory	1.9
	Cardiovascular	1.3
	Small intestine	1.1
	Mouth	1.5
	Thymus	2.8
41 - 50	Lower respiratory	1.3
	Bones	3.0
	Joints	2.6
	Cardiovascular	0.5
	Multi-system	0.9
51 - 60	Small intestine	2.1
	Lower respiratory	1.0
	Cardiovascular	0.5
	Mouth	1.3
	Bones	1.4
61 - 70	Cardiovascular	1.1
	Lower respiratory	0.8
	Small intestine	0.8
	Brain	2.2
71 - 80	Cardiovascular	0.9
	Lower respiratory	0.7
	Small intestine	1.3
	Brain	3.0
81 - 90	Multi-system	2.8
	Small intestine	1.5
	Cardiovascular	0.7
	Lower respiratory	0.4
91 - max.	Cardiovascular	0.6
	Multi-system	1.3
	Small intestine	1.0
	Lower respiratory	0.4

Table IV-44 Biochemical Factor calculated for the most common pathological sites within each regular percentile band for magnesium, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 10	Cardiovascular	1.7
	Multi-system	1.5
	Lower respiratory	0.5
11 - 20	Cardiovascular	1.7
	Lower respiratory	1.4
	Stomach	4.0
	Small intestine	0.6
21 - 30	Cardiovascular	1.6
	Lower respiratory	1.1
	Small intestine	1.3
	Forestomachs	2.7
	Bones	1.5
31 - 40	Lower respiratory	1.6
	Cardiovascular	1.5
	Mouth	1.1
	Small intestine	0.7
	Liver	2.4
41 - 50	Cardiovascular	1.0
	Small intestine	1.6
	Lower respiratory	0.5
51 - 60	Lower respiratory	1.4
	Brain	3.8
	Cardiovascular	0.6
	Multi-system	1.1
61 - 70	Lower respiratory	1.3
	Multi-system	1.2
	Small intestine	1.0
71 - 80	Lower respiratory	0.8
	Cardiovascular	0.7
	Mouth	1.7
	Small intestine	1.0
81 - 90	Lower respiratory	1.3
	Small intestine	1.3
	Multi-system	1.3
	Cardiovascular	0.5
	Thymus	2.7
91 - max.	Small intestine	1.6
	Multi-system	1.6
	Cardiovascular	0.6
	Lower respiratory	0.5
	Bones	1.4
	Lower urinary	6.7

Table IV-45 Biochemical Factor calculated for the most common pathological sites within each regular percentile band for phosphate, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 10	Cardiovascular	1.3
	Lower respiratory	0.7
	Multi-system	1.4
11 - 20	Cardiovascular	0.9
	Multi-system	1.8
	Lower respiratory	0.6
	Mouth	1.6
21 - 30	Lower respiratory	1.5
	Cardiovascular	0.6
	Mouth	1.7
	Bones	1.9
31 - 40	Lower respiratory	2.0
	Cardiovascular	0.7
	Multi-system	0.7
	Small intestine	0.6
	Joints	1.4
	Kidney	1.9
41 - 50	Small intestine	1.4
	Cardiovascular	0.7
	Lower respiratory	0.5
51 - 60	Lower respiratory	1.2
	Cardiovascular	1.1
	Bones	2.9
	Small intestine	1.3
61 - 70	Lower respiratory	1.0
	Cardiovascular	0.9
	Small intestine	1.4
	Skin	5.1
71 - 80	Lower respiratory	1.2
	Cardiovascular	1.2
	Small intestine	1.7
	Multi-system	0.8
81 - 90	Cardiovascular	1.0
	Lower respiratory	0.7
	Multi-system	1.4
	Small intestine	1.0
	Thymus	3.2
91 - max.	Cardiovascular	2.1
	Lower respiratory	1.1
	Multi-system	1.3
	Small intestine	0.9
	Thymus	2.8

Table IV-46 Biochemical Factor calculated for the most common pathological sites within each regular percentile band for aspartate amino-transferase, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 20	Lower respiratory	1.4
	Cardiovascular	0.7
	Small intestine	1.1
	Bones	1.6
	Joints	1.5
	Multi-system	0.6
21 - 30	Multi-system	2.2
	Small intestine	1.6
	Forestomachs	3.9
	Lower respiratory	0.6
	Bones	2.4
31 - 50	Lower respiratory	1.4
	Cardiovascular	0.8
	Multi-system	1.1
	Mouth	1.2
	Small intestine	0.6
51 - 60	Small intestine	2.0
	Lower respiratory	0.9
	Cardiovascular	0.6
	Mouth	1.9
	Brain	2.2
61 - 70	Cardiovascular	1.4
	Multi-system	2.1
	Lower respiratory	1.0
	Mouth	1.8
	Thymus	2.0
71 - 80	Cardiovascular	1.5
	Lower respiratory	0.7
	Serosae	4.3
	Forestomachs	3.6
81 - 90	Cardiovascular	1.3
	Multi-system	2.4
	Lower respiratory	0.6
	Small intestine	1.1
	Mouth	1.2
	Thymus	2.3
91 - max.	Cardiovascular	2.9
	Small intestine	0.8
	Liver	3.4
	Lower respiratory	0.4
	Thymus	2.4

Table IV-47 Biochemical Factor calculated for the most common pathological sites within each regular percentile band for bilirubin, based on data from cattle cases presented to the University of Glasgow Veterinary School.

Percentile band	Most frequent sites	Biochemical Factor
Min. - 10	Lower respiratory	2.1
	Cardiovascular	1.1
	Joints	2.1
11 - 20	Lower respiratory	1.8
	Cardiovascular	0.7
	Multi-system	1.1
	Other	3.9
21 - 30	Cardiovascular	1.3
	Multi-system	1.5
	Lower respiratory	0.6
31 - 40	Lower respiratory	1.3
	Cardiovascular	0.9
	Small intestine	1.5
41 - 50	Cardiovascular	1.4
	Lower respiratory	1.1
	Small intestine	1.1
	Stomach	3.7
51 - 60	Cardiovascular	1.5
	Lower respiratory	0.7
	Small intestine	0.9
61 - 70	Lower respiratory	0.8
	Cardiovascular	0.8
	Small intestine	1.1
	Bones	2.2
71 - 80	Lower respiratory	1.2
	Cardiovascular	0.8
	Multi-system	1.1
	Small intestine	0.9
	Bones	1.8
81 - 90	Small intestine	2.0
	Cardiovascular	0.9
	Multi-system	1.4
	Thymus	3.1
91 - max.	Cardiovascular	1.0
	Small intestine	1.8
	Multi-system	1.3
	Lower respiratory	0.4
	Lower urinary	6.3
	Bones	1.2
	Kidney	3.6

Table IV-48 Biochemical Factor calculated for the most common pathological sites within each regular percentile band for creatinine, based on data from cattle cases presented to the University of Glasgow Veterinary School.

APPENDIX V

BOVINE DISEASE PROFILES

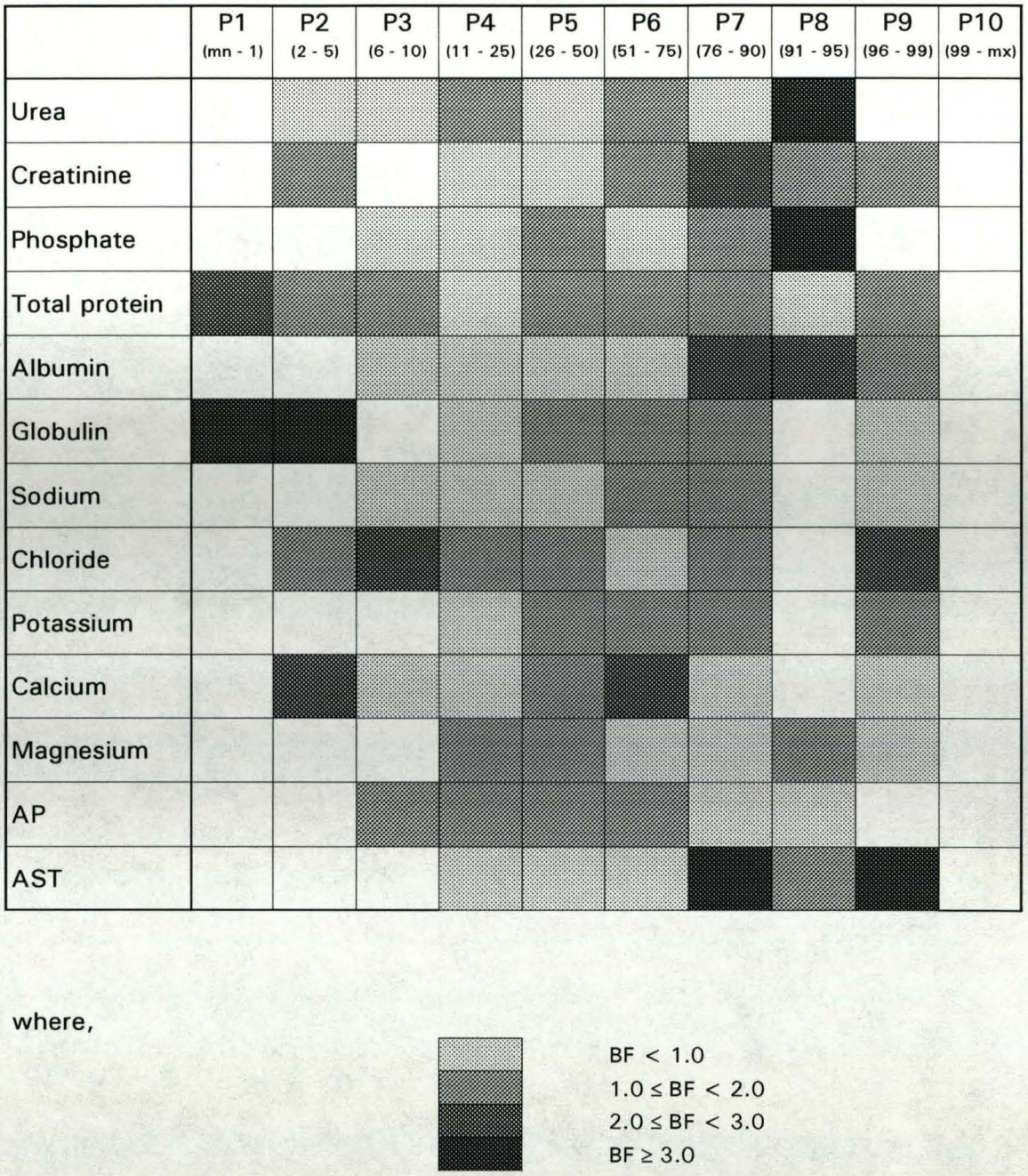

Figure V-1 Clinical biochemistry profile for lymphosarcoma, based on shading from Biochemical Factors calculated using the irregular percentile grouping approach.

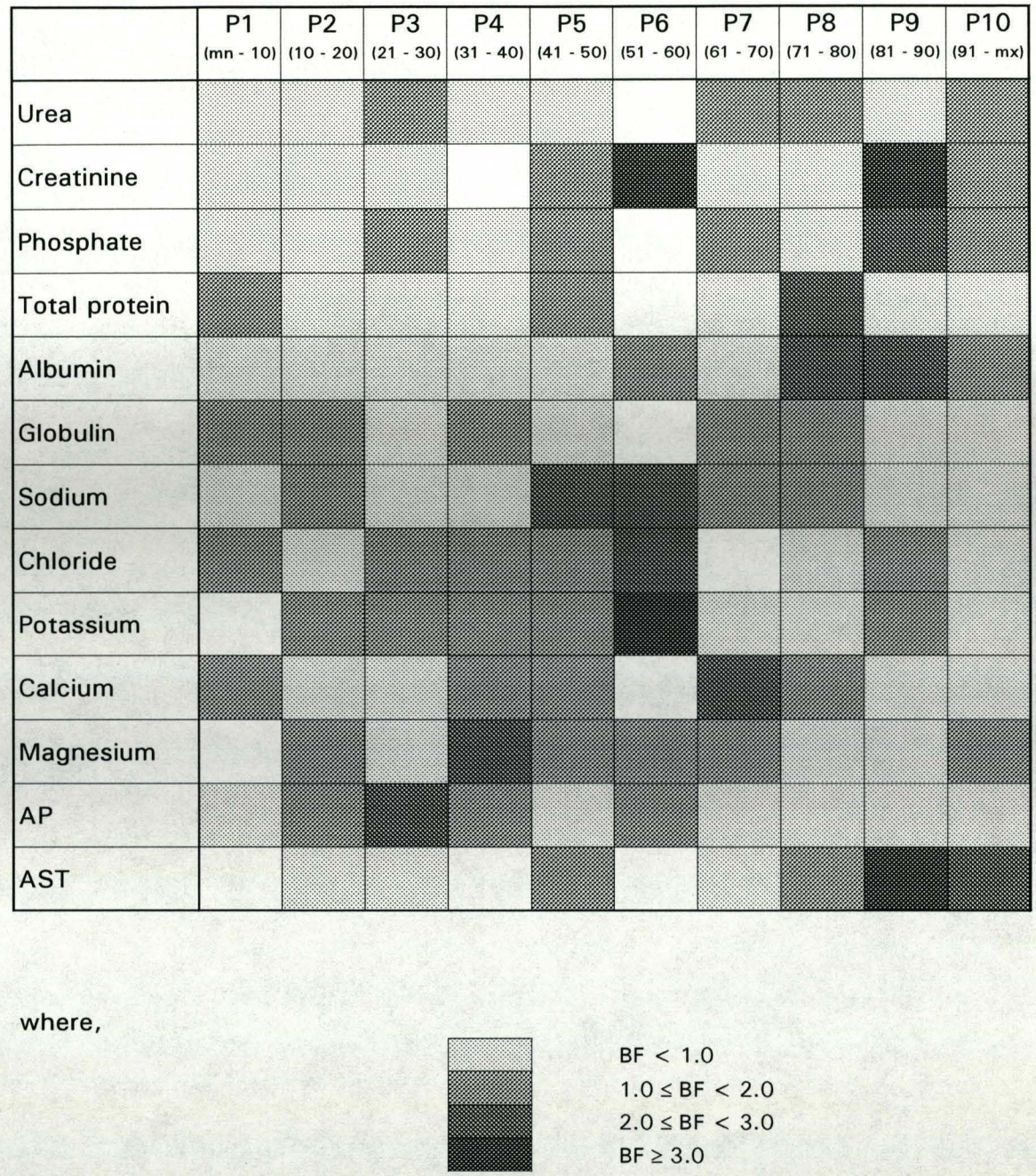

Figure V-2 Clinical biochemistry profile for lymphosarcoma, based on shading from Biochemical Factors calculated using the regular percentile grouping approach.

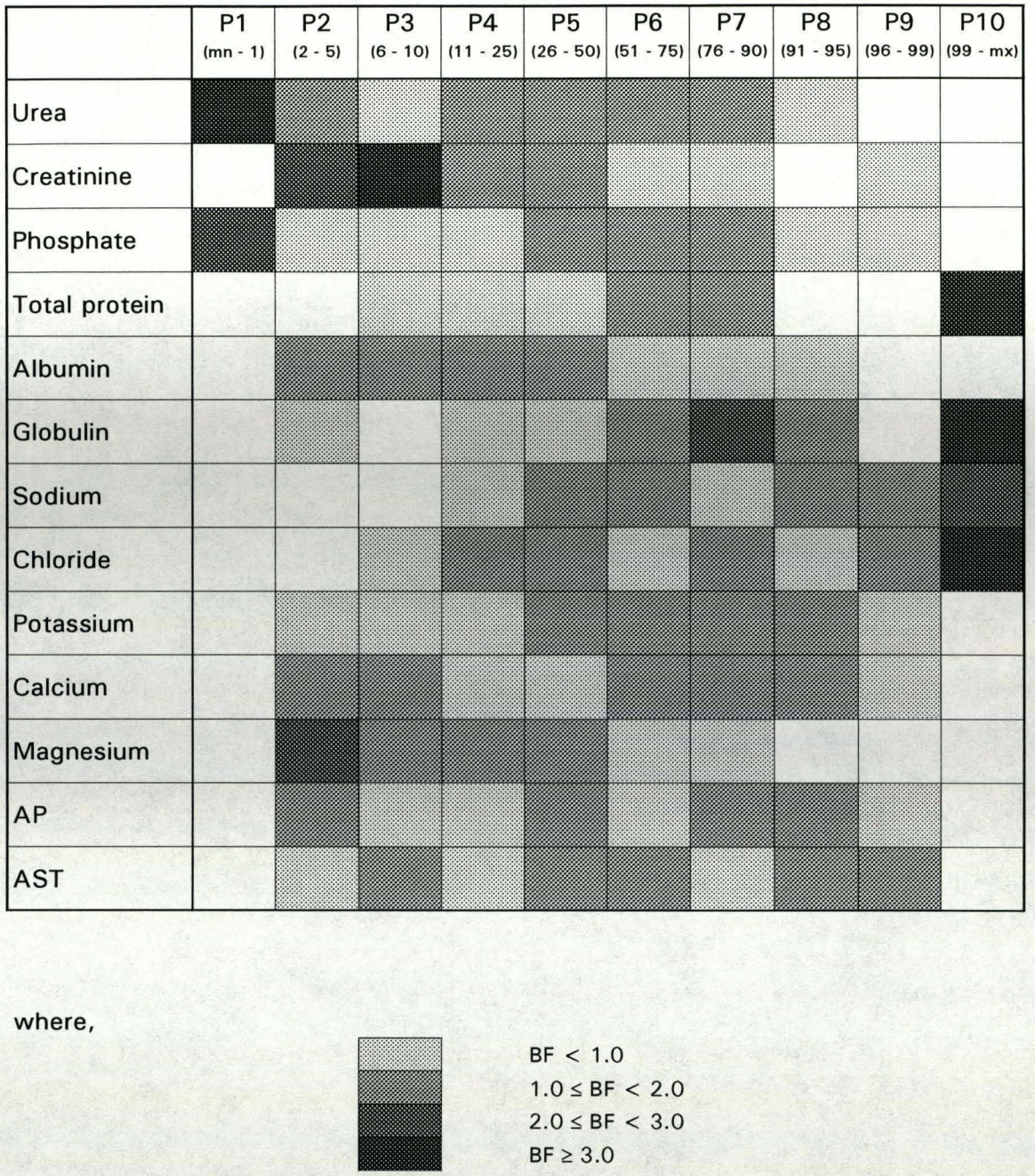

Figure V-3 Clinical biochemistry profile for chronic suppurative pulmonary disease, based on shading from Biochemical Factors calculated using the irregular percentile grouping approach.

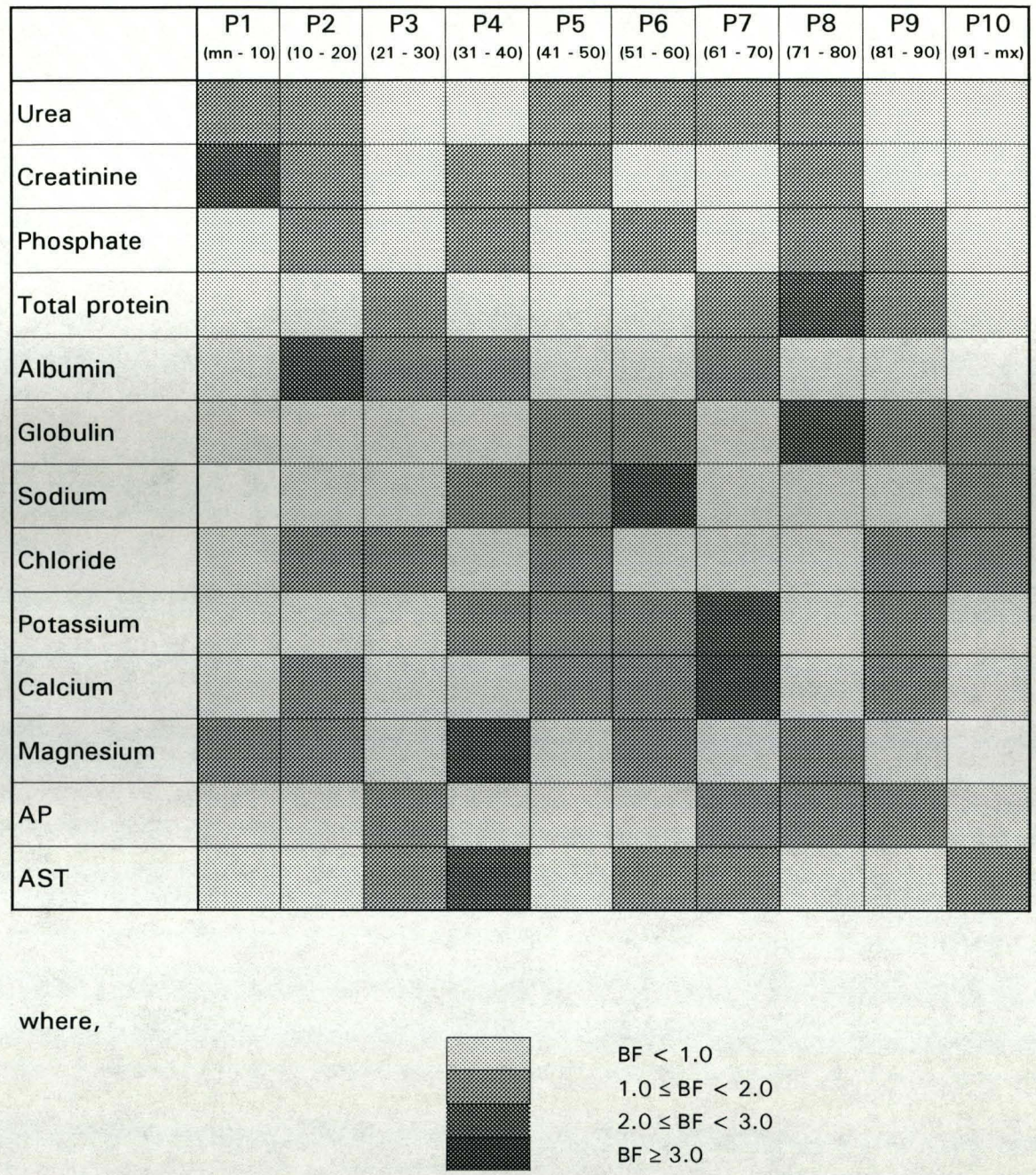

Figure V-4 Clinical biochemistry profile for chronic suppurative pulmonary disease, based on shading from Biochemical Factors calculated using the regular percentile grouping approach.

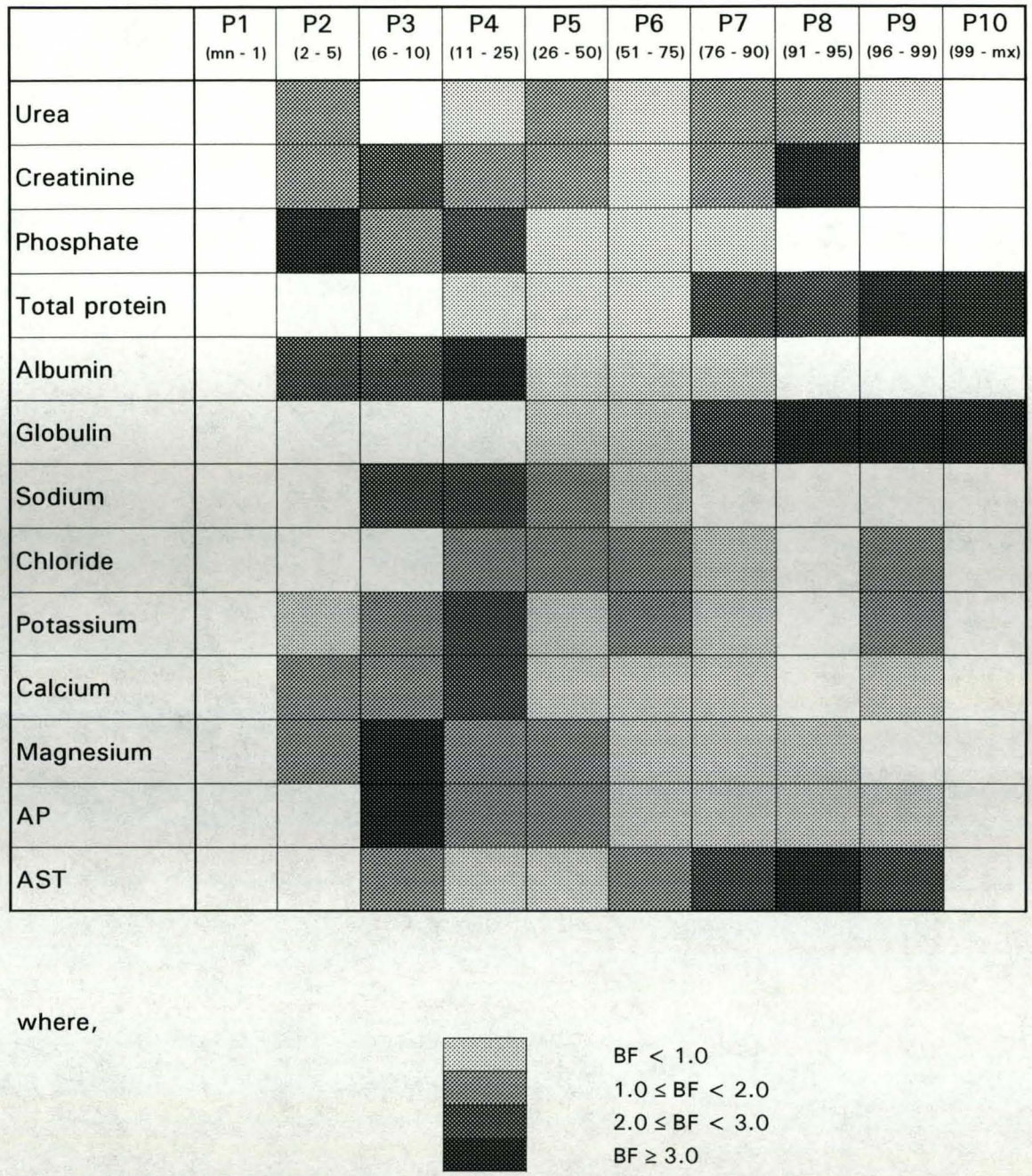

Figure V-5 Clinical biochemistry profile for endocarditis, based on shading from Biochemical Factors calculated using the irregular percentile grouping approach.

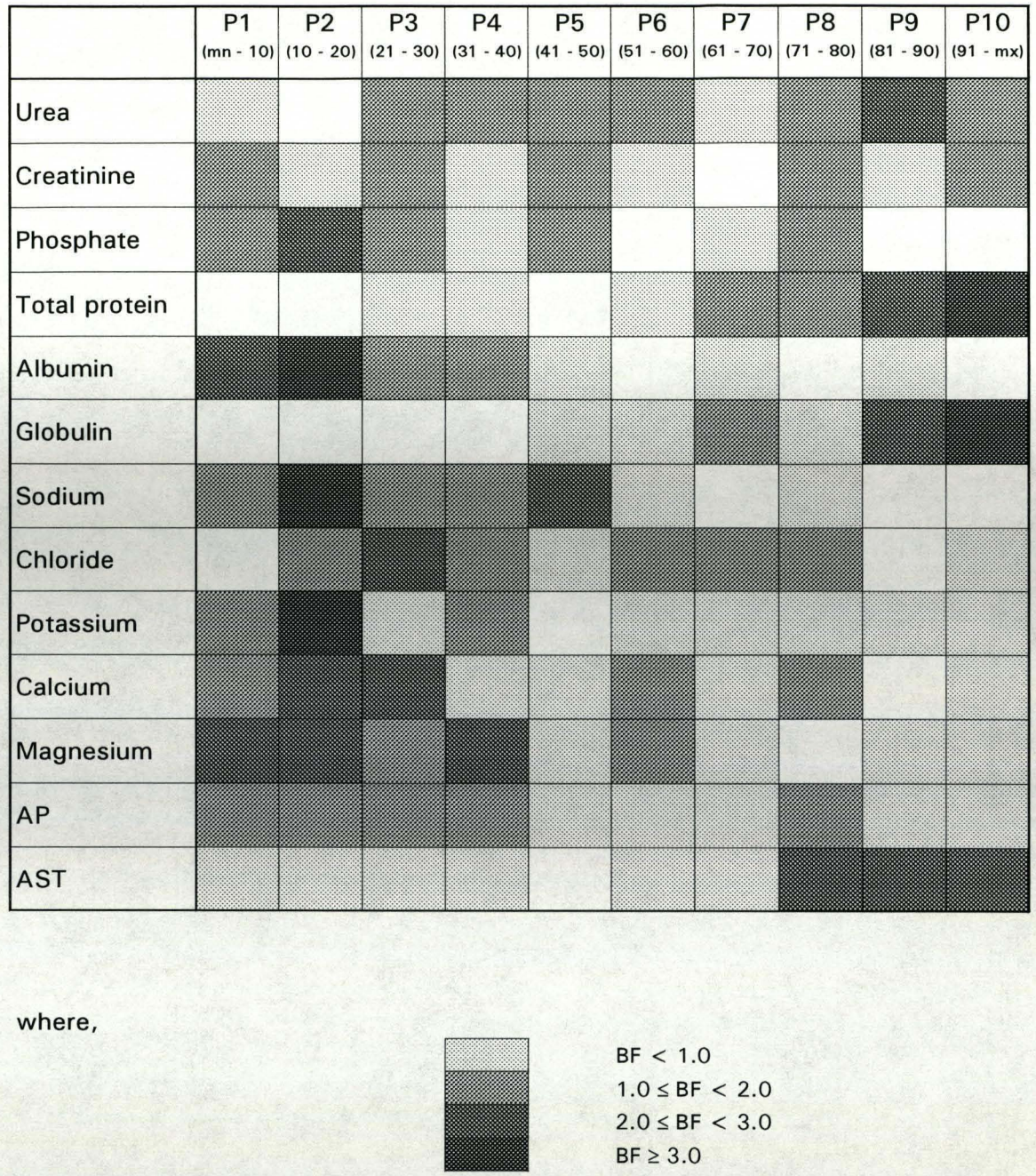

Figure V-6 Clinical biochemistry profile for endocarditis, based on shading from Biochemical Factors calculated using the regular percentile grouping approach.

APPENDIX VI

DATA FOR ROC CURVES

Cut-off value	Specificity	1-Specificity	Sensitivity
0	0.0	100.0	100.0
2	16.0	84.0	100.0
4	32.0	68.0	100.0
6	36.0	64.0	100.0
8	38.0	62.0	100.0
10	52.0	48.0	100.0
12	58.0	42.0	100.0
14	64.0	36.0	100.0
16	74.0	26.0	100.0
21	76.0	24.0	100.0
22	78.0	22.0	96.8
23	80.0	20.0	96.8
25	88.0	12.0	96.8
27	92.0	8.0	96.8
29	94.0	6.0	96.8
30	98.0	2.0	96.8
31	100.0	0.0	96.8
36	100.0	0.0	93.5
38	100.0	0.0	87.1
42	100.0	0.0	83.9
44	100.0	0.0	74.2
55	100.0	0.0	64.5
60	100.0	0.0	51.6
65	100.0	0.0	48.4
70	100.0	0.0	45.2
75	100.0	0.0	35.5
80	100.0	0.0	25.8
85	100.0	0.0	19.4
90	100.0	0.0	16.1
95	100.0	0.0	12.9
150	100.0	0.0	9.7
200	100.0	0.0	3.2
213	100.0	0.0	0.0

Table VI-1 Sensitivity and specificity of serum amyloid-A (SAA) (mg/l) used to differentiate between cattle with acute and chronic inflammation, calculated at a range of cut-off values.

Cut-off value	Specificity	1-Specificity	Sensitivity
50	0.0	100.0	100.0
54	2.1	97.9	100.0
55	4.2	95.8	100.0
61	8.3	91.7	100.0
64	12.5	87.5	100.0
65	14.6	85.4	100.0
66	16.7	83.3	96.6
67	18.8	81.2	93.1
68	22.9	77.1	93.1
69	25.0	75.0	93.1
70	33.3	66.7	93.1
72	35.4	64.6	93.1
73	39.6	60.4	93.1
74	43.8	56.2	93.1
75	47.9	52.1	89.7
76	54.2	45.8	89.7
77	56.3	43.7	86.2
78	58.3	41.7	86.2
80	60.4	39.6	82.8
81	62.5	37.5	75.9
83	66.7	33.3	75.9
84	70.8	29.2	75.9
85	75.0	25.0	72.4
86	79.2	20.8	72.4
87	83.3	16.7	72.4
88	85.4	14.6	69.0
89	85.4	14.6	62.1
90	85.4	14.6	55.2
91	85.4	14.6	41.4
92	87.5	12.5	41.4
93	89.6	10.4	34.5
94	93.8	6.2	34.5
97	95.8	4.2	34.5
100	95.8	4.2	31.0
101	95.8	4.2	27.6
103	95.8	4.2	24.1
105	95.8	4.2	20.7
106	95.8	4.2	17.2
107	97.9	2.1	13.8
110	97.9	2.1	10.3
115	100.0	0.0	6.9
117	100.0	0.0	3.4
118	100.0	0.0	0.0

Table VI-2 Sensitivity and specificity of total protein (TP) (g/l) used to differentiate between cattle with acute and chronic inflammation, calculated at a range of cut-off values.

Cut-off value	Specificity	1-Specificity	Sensitivity
1.86	0.0	100.0	100.0
1.90	0.0	100.0	96.4
1.94	2.1	97.9	96.4
1.98	4.2	95.8	96.4
2.02	6.3	93.7	96.4
2.06	8.3	91.7	92.9
2.10	16.7	83.3	89.3
2.14	27.1	72.9	89.3
2.18	31.3	68.7	89.3
2.22	33.3	66.7	85.7
2.26	41.7	58.3	75.0
2.30	47.9	52.1	75.0
2.34	52.1	47.9	67.9
2.38	58.3	41.7	57.1
2.42	66.7	33.3	50.0
2.46	75.0	25.0	39.3
2.50	85.4	14.6	39.3
2.54	87.5	12.5	28.6
2.58	93.8	6.2	17.9
2.62	95.8	4.2	17.9
2.66	97.9	2.1	17.9
2.70	97.9	2.1	17.9
2.74	97.9	2.1	3.6
2.78	97.9	2.1	3.6
2.82	97.9	2.1	3.6
2.86	100.0	0.0	0.0

Table VI-3 Sensitivity and specificity of calcium (mmol/l) used to differentiate between cattle with acute and chronic inflammation, calculated at a range of cut-off values.

Cut-off value	Specificity	1-Specificity	Sensitivity
0.0	0.0	100.0	100.0
1.0	72.0	28.0	41.9
1.5	78.0	22.0	38.7
2.0	80.0	20.0	38.7
2.5	86.0	14.0	38.7
3.0	88.0	12.0	38.7
4.0	88.0	12.0	35.5
4.5	92.0	8.0	35.5
7.0	92.0	8.0	29.0
9.0	94.0	6.0	29.0
10.0	96.0	4.0	29.0
11.0	96.0	4.0	25.8
12.5	96.0	4.0	19.4
13.5	98.0	2.0	19.4
14.0	100.0	0.0	19.4
17.0	100.0	0.0	16.1
18.5	100.0	0.0	12.9
24.0	100.0	0.0	9.7
38.0	100.0	0.0	6.5
52.0	100.0	0.0	3.2
53.0	100.0	0.0	0.0

Table VI-4 Sensitivity and specificity of band polymorphonuclear leukocytes (BPMN) (%) used to differentiate between cattle with acute and chronic inflammation, calculated at a range of cut-off values.

Cut-off value	Specificity	1-Specificity	Sensitivity
1.5	0.0	100.0	100.0
2.0	2.1	97.9	100.0
2.5	2.1	97.9	100.0
3.0	2.1	97.9	100.0
3.5	2.1	97.9	96.8
4.0	2.1	97.9	93.5
4.5	4.2	95.8	83.9
5.0	10.4	89.6	74.2
5.5	20.8	79.2	64.5
6.0	31.3	68.7	58.1
6.5	35.4	64.6	48.4
7.0	41.7	58.3	35.5
7.5	50.0	50.0	29.0
8.0	52.1	47.9	22.6
8.5	58.3	41.7	16.1
9.0	62.5	37.5	16.1
9.5	66.7	33.3	9.7
10.0	75.0	25.0	9.7
10.5	77.1	22.9	9.7
11.0	77.1	22.9	3.2
11.5	81.3	18.7	3.2
12.0	85.4	14.6	3.2
12.5	91.7	8.3	3.2
13.0	93.8	6.2	3.2
13.5	93.8	6.2	3.2
14.0	93.8	6.2	3.2
14.5	95.8	4.2	3.2
15.0	97.9	2.1	3.2
15.5	97.9	2.1	3.2
16.0	100.0	0.0	3.2
16.5	100.0	0.0	0.0

Table VI-5 Sensitivity and specificity of red blood cell count (RBC) ($x10^{12}$/l) used to differentiate between cattle with acute and chronic inflammation, calculated at a range of cut-off values.

APPENDIX VII

DETAILS OF GUVS BIOCHEMISTRY ANALYSERS

CONE
Lab Medics Limited
Green Lane
Romily
Stockport
Cheshire SK6 3JQ

COBAS-MIRA DISCRETE ANALYSER
Roche Diagnostics
40 Broadwater Road
Welwyn Garden City
Hertfordshire AL7 3AY

ATOMIC ABSORPTIOMETER/SPECTROPHOTOMETER 257 (Ca/Mg)
FLAME PHOTOMETRY 543 (Na/K)
Instrumentation Laboratory UK Limited
Kelvin Close
Birchwood Science Park
Warrington
Cheshire WA3 7PB

CORNING CHLORIDE ANALYSER 925 (Cl)
Chiron Diagnostics Limited
Northern Road
Sudbury
Suffolk CO10 6XQ

AXON DISCRETE ANALYSER
Bayer Diagnostics
Bayer Plc.
Bayer House
Strawberry Hill
Newbury
Berkshire RG14 1JA

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British Medical Journal (1998) http://www.bmj.com/bmj/

Britton's Wise Computers (1996) http://www.bwci.com/bwc/pages/software.htm#AHMS

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